

CADTH

pCODR

PAN-CANADIAN
ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review Final Clinical Guidance Report

Apalutamide (Erleada) for Castration-Resistant Prostate Cancer

November 1, 2018

DISCLAIMER

Not a Substitute for Professional Advice

This report is primarily intended to help Canadian health systems leaders and policymakers make well-informed decisions and thereby improve the quality of health care services. While patients and others may use this report, they are made available for informational and educational purposes only. This report should not be used as a substitute for the application of clinical judgment in respect of the care of a particular patient or other professional judgment in any decision making process, or as a substitute for professional medical advice.

Liability

pCODR does not assume any legal liability or responsibility for the accuracy, completeness or usefulness of any information, drugs, therapies, treatments, products, processes, or services disclosed. The information is provided "as is" and you are urged to verify it for yourself and consult with medical experts before you rely on it. You shall not hold pCODR responsible for how you use any information provided in this report.

Reports generated by pCODR are composed of interpretation, analysis, and opinion on the basis of information provided by pharmaceutical manufacturers, tumour groups, and other sources. pCODR is not responsible for the use of such interpretation, analysis, and opinion. Pursuant to the foundational documents of pCODR, any findings provided by pCODR are not binding on any organizations, including funding bodies. pCODR hereby disclaims any and all liability for the use of any reports generated by pCODR (for greater certainty, "use" includes but is not limited to a decision by a funding body or other organization to follow or ignore any interpretation, analysis, or opinion provided in a pCODR report).

FUNDING

The pan-Canadian Oncology Drug Review is funded collectively by the provinces and territories with the exception of Quebec, which does not participate in pCODR at this time.

INQUIRIES

Inquiries and correspondence about the pan-Canadian Oncology Drug Review (pCODR) should be directed to:

pan-Canadian Oncology Drug Review
154 University Avenue, Suite 300
Toronto, ON
M5H 3Y9

Telephone: 613-226-2553
Toll Free: 1-866-988-1444
Fax: 1-866-662-1778
Email: info@pcodr.ca
Website: www.cadth.ca/pcodr

LIST OF ABBREVIATIONS

ADT	Androgen deprivation therapy
AE	Adverse event
AR	Androgen receptor
BICR	Blinded independent central review
CI	Confidence interval
CNS	Central nervous system
CRPC	Castration Resistant Prostate Cancer
ECOG	Eastern Cooperative Oncology Group
FACT-G	Functional Assessment of Cancer Therapy-General
FACT-P	Functional Assessment of Cancer Therapy-Prostate
FDA	Food and Drug Administration of the United States
GnRH	Gonadotropin-releasing hormone
HR	Hazard ratio
ITT	Intent-to-treat population
IV	Intravenous
IVRS	Interactive Voice Response System
mCRPC	Metastatic castration-resistant prostate cancer
MFS	Metastasis-free survival
nmCRPC	Non-metastatic castration-resistant prostate cancer
OS	Overall survival
PFS	Progression-free survival
PFS2	Progression-free survival during first subsequent therapy
PSA	Prostate-specific antigen
PSADT	Prostate-specific antigen doubling time
HRQoL	Health-related quality of life
SAE	Serious adverse event
US	United States of America

TABLE OF CONTENTS

DISCLAIMER AND FUNDING	ii
INQUIRIES	iii
LIST OF ABBREVIATIONS	iv
TABLE OF CONTENTS	v
1 GUIDANCE IN BRIEF	1
1.1 Introduction	1
1.2 Key Results and Interpretation	1
1.2.1 Systematic Review Evidence	1
1.2.2 Additional Evidence	4
1.2.3 Factors Related to Generalizability of the Evidence	6
1.2.4 Interpretation	10
1.3 Conclusions	13
2 BACKGROUND CLINICAL INFORMATION	15
2.1 Description of the Condition.....	15
2.2 Accepted Clinical Practice	15
2.3 Evidence-Based Considerations for a Funding Population.....	15
2.4 Other Patient Populations in Whom the Drug May Be Used.....	17
3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT	19
3.1 Condition and Current Therapy Information	20
3.1.1 Experiences Patients have with CRPC	19
3.1.2 Patients’ Experiences with Current Therapy for CRPC.....	22
3.1.3 Impact of CRPC and Current Therapy on Caregivers	22
3.2 Information about the Drug Being Reviewed.....	25
3.2.1 Patient Expectations for and Experiences To Date with Apalutamide	25
3.2.2 Additional Information.....	25
4 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT	27
4.1 Factors Related to Comparators	26
4.2 Factors Related to Patient Population	26
4.3 Factors Related to Dosing	27
4.4 Factors Related to Implementation Costs	27
4.5 Factors Related to Health System	27
4.6 Factors Related to Manufacturer	27
5 SUMMARY OF REGISTERED CLINICIAN INPUT	29
5.1 Current Treatment(s) for CRPC	28
5.2 Eligible Patient Population.....	28
5.3 Relevance to Clinical Practice	28
5.4 Sequencing and Priority of Treatments with Apalutamide.....	29
5.5 Companion Diagnostic Testing	29
5.6 Additional Information.....	29
6 SYSTEMATIC REVIEW	31
6.1 Objectives	31
6.2 Methods	31
6.3 Results	33
6.3.1 Literature Search Results.....	33
6.3.2 Summary of Included Studies	34
6.4 Ongoing Trials.....	34
7 SUPPLEMENTAL QUESTIONS.....	58
8 COMPARISON WITH OTHER LITERATURE	60
9 ABOUT THIS DOCUMENT	61
APPENDIX A: LITERATURE SEARCH STRATEGY AND DETAILED METHODOLOGY	62
REFERENCES	66

1 GUIDANCE IN BRIEF

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding apalutamide (Erleada) for non-metastatic castration resistant prostate cancer. The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the CADTH website (www.cadth.ca/pcodr).

This Clinical Guidance is based on: a systematic review of the literature regarding apalutamide (Erleada) for non-metastatic castration resistant prostate cancer conducted by the Genitourinary Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; input from Registered Clinicians; and supplemental issues relevant to the implementation of a funding decision.

The systematic review and supplemental issues are fully reported in Sections 6 and 7. A background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input on apalutamide (Erleada) for non-metastatic castration resistant prostate cancer, a summary of submitted Provincial Advisory Group Input on apalutamide (Erleada) for non-metastatic castration resistant prostate cancer, and a summary of submitted Registered Clinician Input on apalutamide (Erleada) for non-metastatic castration resistant prostate cancer, are provided in Sections 2, 3, 4, and 5 respectively.

1.1 Introduction

The purpose of this review is to evaluate the efficacy and safety of apalutamide (Erleada) in combination with androgen deprivation therapy (ADT) compared to ADT alone in men with non-metastatic castrate resistant prostate cancer (nm-CRPC).

Apalutamide is a next-generation androgen receptor inhibitor that binds to the ligand-binding domain of the androgen receptor, a mechanism that is distinct from the first generation anti-androgens. Apalutamide reduces proliferation of castration-resistant prostate cancer cells and increases apoptosis and necrosis. Apalutamide has a Health Canada indication that reflects the requested patient population for reimbursement. Apalutamide has been issued marketing authorization without conditions for patients with nmCRPC. The Health Canada Product Monograph (PM) also notes that apalutamide has not been studied in patients with nmCRPC at low risk of developing metastases and that the benefit and risk profile in these patients is unknown.

The Health Canada recommended dose of apalutamide (Erleada) is 240 mg (four 60 mg tablets) administered orally once daily. The Health Canada PM notes that patients should also receive a gonadotropin-releasing hormone (GnRH) analog concurrently or should have had bilateral orchiectomy and that apalutamide should be permanently discontinued in patients who develop a seizure during treatment.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

The pCODR systematic review included one randomized-controlled trial (RCT). The results of the SPARTAN trial (N=1207) will be presented below:

SPARTAN

The SPARTAN trial (n =1207) was a multicentre, randomized, double-blind, placebo-controlled phase 3 trial that enrolled adult patients with a histologically or cytologically confirmed castration-resistant prostate cancer who were in high risk for development of metastases (prostate-specific antigen doubling time [PSADT] \leq 10 months, during continuous ADT). To be eligible for inclusion in the trial, patients had to have testosterone levels of less than 50 ng/dL, and no evidence of symptomatic local or regional nodal disease, no malignant pelvic lymph nodes $>$ 2 cm in the short axis, no prior treatment with next generation anti-androgens, and an Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1.¹⁻³

Patients were randomly assigned to receive either apalutamide (240 mg once daily) or placebo using a 2:1 ratio randomization was stratified by PSADT ($>$ 6 months vs. \leq 6 months), use of bone sparing agents (yes vs. no), and presence of loco-regional disease (N0 vs N1).^{1,4}

The primary outcome of the study was metastasis-free survival (MFS), as assessed by BICR. Secondary outcomes included: time to metastasis (as assessed by BICR), progression-free survival (PFS; as assessed by BICR), time to symptomatic progression, overall survival (OS), and time to the initiation of cytotoxic chemotherapy. Exploratory outcomes included time to PSA progression, PSA response rate, quality of life outcomes, second-progression-free survival, and treatment-emergent adverse events (TEAEs).^{1,2}

Demographic and baseline characteristics were well balanced between the study groups. The median age in the ITT population was 74 years (range 48-94 years in the apalutamide arm and 52-97 in the placebo arm). The median PSA doubling time at baseline was 4.4 months in the apalutamide arm and 4.5 months in the placebo arm. The median time from initial prostate cancer diagnosis to randomization was 7.95 years in the apalutamide arm and 7.85 years in the placebo arm. About 10% of patients in each arm had a history of treatment with a bone sparing agent, and around 16% of patients in each arm presented with lymph nodes ($<$ 2cm).¹

Efficacy

The key efficacy outcomes of the SPARTAN trial are presented in Table 1.1.^{1,3} As of 19-May-2017 data cut-off date, after a median follow-up time of 20.3 months:

- Distant metastasis or death had been observed in 184 patients (22.8%) in the apalutamide arm and 194 patients (48.4%) in the placebo arm. Treatment with apalutamide significantly decreased the risk of distant metastasis or death, when compared with placebo (hazard ratio [HR] = 0.28; 95% CI 0.23, 0.35; $P <$ 0.001).
- MFS benefit was consistent across pre-specified subgroups based on patient's ECOG performance status, age groups, geographic region, number of prior hormonal therapies, baseline PSA value, PSADT, bone-sparing agent use, and loco-regional disease. No outliers were observed in the subgroup analysis; however, for the subgroup of Black men (HR = 0.63; 95% CI 0.23, 1.72) the 95% confidence interval of MFS HR crossed 1.00, which indicates a statistically non-significant treatment effect in this subgroup. These results should be interpreted as hypothesis-generating, due to the small size of the subgroups and the exploratory nature of the subgroup analyses. More details are provided in Figure 6.5.
- The median estimate of BIRC-assessed time to metastasis was 40.5 months (95% CI not estimable) in the apalutamide arm and 16.6 months (95% CI 14.6, 18.5) in the placebo arm (HR = 0.27; 95% CI 0.22, 0.34; $p <$ 0.001).
- The median PFS was 40.5 months (95% CI not estimable) for the apalutamide arm and 14.7 months (95% CI 14.5, 18.4) for the placebo arm (HR=0.29; 95% CI: 0.24, 0.36; $p <$ 0.0001). At 12 months, 85% of patients in the apalutamide arm and 56% of those in the placebo arm were progression-free.

- Approximately 8% of patients in the apalutamide arm and 16.0% of those in the placebo arm had symptomatic progression. The median time to symptomatic progression was not reached in either of the apalutamide or placebo arms. However, the analysis of time to event data showed a statistically significant decrease in risk of symptomatic progression in the apalutamide arm, when compared with placebo (stratified HR=0.45; 95% CI: 0.32, 0.63; p<0.0001).
- At the data cut-off date, 62 deaths (7.7%) had occurred in the apalutamide arm and 42 deaths (10.0%) in the placebo arm. The median OS was not reached in the apalutamide arm and was 39.0 months in the placebo arm (HR=0.700; 95% CI: 0.472, 1.038; p=0.0742).

Quality of Life

Health-related quality of life (HRQoL) was assessed using FACT-P (for physical well-being, social/family well-being, emotional well-being, pain and prostate cancer specific symptoms) and EQ-5D (for health status, mobility, self-care, usual activity, pain or discomfort, and anxiety and depression) questionnaires.² Patients experiencing a 10-point decline in FACT-P total scores from baseline were considered to be experiencing a clinically meaningful deterioration in functional status. The decrement in the FACT-P total score was statistically significant compared between treatment arms. The results of EQ-5D questionnaire was reported descriptively.³

Baseline FACT-P and EQ-5D scores were reported to be comparable between the study arms. No statistically significant differences were reported between the apalutamide and placebo arms in change from baseline in FACT-P or EQ-5D scores, during the treatment and follow-up phases.³

Harms

As of the 19-May-2017 data cut-off date, TEAEs (any grade) were reported in 96.5% of patients in the apalutamide arm and in 93.2% of those in the placebo arm. The most frequently reported TEAEs included fatigue (30% with apalutamide versus 21% with placebo), hypertension (25% with apalutamide versus 20% with placebo), skin rash (24% with apalutamide versus 5.5% with placebo), diarrhea (20% with apalutamide versus 15% with placebo), falls (16% with apalutamide versus 9% with placebo), fractures (12% with apalutamide versus 6.5% with placebo), and hypothyroidism (2% with apalutamide versus 8% with placebo).³

The proportion of patients with grade 3 or 4 TEAEs was 45.1% in the apalutamide arm and 34.2% in the placebo arm. Mortality due to AEs was reported in 1.2% of patients in the apalutamide arm and 0.3% of those in the placebo arm; and serious TEAEs occurred in 24.8% and 23.1% of patients in the apalutamide and placebo arms, respectively. As of the data cut-off date, 10.36% of patients in the apalutamide arm and 7.0% of those in the placebo arm had discontinued treatment due to incidence of adverse events (Table 1.1).

Table 1.1: Highlights of Key Outcomes in SPARTAN trial

Efficacy outcomes ^{1,3}	ITT population	
	Apalutamide (N= 806)	Placebo (N= 401)
Primary Outcome		
MFS		
Number of events (%)	184 (22.8)	194 (48.4)
Median MFS, months (95% CI)	40.5 (NE, NE)	16.2 (14.6, 18.4)
HR (95%CI)	0.28 (0.23, 0.35)	
p-value	<0.0001	

	ITT population	
Efficacy outcomes ^{1,3}	Apalutamide (N= 806)	Placebo (N= 401)
Key Secondary Outcomes		
TTM		
Number of events (%)	175 (22)	191 (48)
Median TTM, months (95% CI)	40.5 (NE, NE)	16.6 (14.6, 18.5)
HR (95%CI)	0.27 (0.22, 0.34)	
p-value	<0.0001	
PFS		
Number of events (%)	200 (25.0)	204 (51.0)
Median PFS, months (95% CI)	40.5 (NE, NE)	14.7 (14.5, 18.4)
HR (95%CI)	0.29 (0.24, 0.36)	
p-value	<0.0001	
Time to symptomatic progression		
Number of events (%)	64 (7.9)	63 (16.0)
Median, months (95% CI)	NE (NE, NE)	NE (36.8, NE)
HR (95%CI)	0.45 (0.32, 0.63)	
p-value	<0.0001	
OS		
Number of events (%)	62 (7.7)	42 (10.5)
Median, months (95% CI)	NE (NE, NE)	39.03 (39.0, NE)
HR (95%CI)	0.70 (0.47, 1.04)	
p-value	0.07	
HRQoL*³	Apalutamide (N= 806)	Placebo (N= 401)
FACT-P total score		
median (95% CI)	6.6 (5.6, 7.9)	8.38 (6.5, 12.9)
HR (95%CI)	1.062 (0.904, 1.247)	
p-value	NS	
Safety Population		
Harms Outcome,^{1,3}	Apalutamide (N= 803)	Placebo (N= 398)
n (%)		
TEAEs	775 (96.5)	371 (93.2)
Drug-related TEAEs	565 (70.4)	216 (54.3)
Grade 3-4 TEAEs	362 (45.1)	136 (34.2)
SAEs	199 (24.8)	92 (23.1)
WDAE	85 (10.6)	28 (7.0)
Death due to AEs	10 (1.2)	1 (0.3)
AE = adverse event, CI = confidence interval, HR = hazard ratio, HRQoL = health-related quality of life; ITT = intent-to treat; MFS = metastasis-free survival; NE=not estimable; NR = not reported, NS = non-significant; SD = standard deviation, TEAE = treatment-emergent adverse event, TTM = time to metastasis; WDAE = withdrawal due to adverse event		
*EQ-5D questionnaire was also used: no differences between the apalutamide and placebo arms were observed in change from baseline across the EQ-5D dimensions or EQ-VAS. HR < 1 favours apalutamide arm		

1.2.2 Additional Evidence

See Section 3, Section 4, and Section 5 for a complete summary of patient advocacy group input, Provincial Advisory Group (PAG) Input, and Registered Clinician Input, respectively.

Patient Advocacy Group Input

Three patient advocacy groups, PROSTAID Calgary, the Canadian Cancer Survivor Network (CCSN), and the Prostate Cancer Centre (PCC), provided input on the apalutamide

(Erleada) submission for the treatment of non-metastatic castration resistant prostate cancer

From a patient's perspective, there were a number of negative sentiments about patient's experiences with prostate cancer. The following issues were perceived by the survey participants to have a negative impact on quality of life: challenges with intimacy and sexual dysfunction, patients' negative psychological feelings regarding their "manhood", and urinary incontinence.

There were a number of quotes from PROSTAID Calgary asserting feelings that physicians are biased towards surgical treatment options, and that patients are not given opportunities to consider alternative treatment methods. The survey results suggested that patients felt strongly about being given treatment options other than surgery.

In terms of expectations for alternative treatment options, focus was placed on improving quality of life and managing or reducing side effects. Patients reported feeling anxious about whether they will qualify for further treatment, and worrying about how prostate cancer will affect their future.

In total, seven respondents indicated having experience with apalutamide. Two patients did not experience any side effects related to apalutamide, and the remaining five reported minimal, only one or two, side effects, including hot flashes, reduced bone density, lowered PSA levels, and increased fatigue. Relative to the experienced side effects, participants had an overall positive attitude toward apalutamide; the benefits of the drug were considered to outweigh the risk of the side effects.

Provincial Advisory Group (PAG) Input

Input was obtained from all nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation:

Clinical factors:

- Clarity of eligible patient population.
- Appropriate treatments for metastatic, castration resistant disease after apalutamide.

Economic factors:

- Add-on therapy to androgen deprivation therapy.

Registered Clinician Input

Six clinician inputs were provided: 4 from individual oncologists and 2 group inputs.

The clinicians providing input all expressed that there is currently no funded standard of care for patients with non-metastatic castration resistant prostate cancer (nmCRPC) and that apalutamide does fill an unmet need. It was noted repeatedly that there is a gap in treatment options for patients in this stage of disease because patients must progress to having metastatic disease before they are eligible to receive most treatment options. In terms of sequencing, it was reported by the clinicians that apalutamide would be used in combination with androgen deprivation therapy (ADT), before a nmCRPC patient has developed metastases. It was noted that adding apalutamide to the available drug options may affect which treatment a patient receives if they become metastatic. There is no diagnostic testing required for this drug.

Summary of Supplemental Questions

There were no supplemental questions identified for this review.

Comparison with Other Literature

The pCODR Clinical Guidance Panel and the pCODR Methods Team did not identify other relevant literature providing supporting information for this review.

1.2.3 Factors Related to Generalizability of the Evidence

Table 2 addresses the generalizability of the evidence and an assessment of the limitations and sources of bias can be found in Sections 6.3.2.1a and 6.3.2.1b (regarding internal validity).

Table 2: Assessment of generalizability of evidence for regarding apalutamide for non-metastatic castration resistant prostate cancer

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
Population	Performance status	The included trial limited eligibility to patients with an ECOG performance status of 0 or 1.	Does performance status limit the interpretation of the trial results (efficacy or toxicity) with respect to the target population (e.g., Canadian clinical practice, patients without the factor, etc.)?	The benefit for patients with ECOG 2 cannot be formally concluded from the study, however it would be reasonable to expand apalutamide to patients with a good performance status, based on clinical experience and the manageable side-effect profile of similar drugs in the metastatic CRPC setting.
	Risk of metastasis	SPARTAN required study participants to be at high risk for development of metastases, defined as PSADT \leq 10 months, during continuous ADT.	Are the results of the trial generalizable to patients with PSADT $>$ 10 months?	Interpretation of the trial results applies to patients at high risk for progression as defined in the SPARTAN trial (PSADT \leq 10 months). There are no data to support use of apalutamide in patients with PSADT $>$ 10 months. Patients without the high risk features as defined in the SPARTAN trial can have prolonged, indolent course of disease and it is unclear how much benefit they would derive from apalutamide.

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
				As such the SPARTAN results cannot be generalized to high risk patients (e.g., Gleason score 8-10, high PSA at diagnosis, etc.) who have not had a PSA progression in the non-metastatic setting.
	Definition of castration resistant prostate cancer	SPARTAN required that patients have three PSA rises at least one week apart with the last PSA more than 2 ng/ml.	If different criteria are used to define castration resistance in the Canadian practice, are the results of the trial applicable in the Canadian setting?	<p>The CGP feels that the definition of castration resistant prostate cancer used in the SPARTAN trial is clinical reasonable, based on available evidence, and applies to the Canadian practice setting.</p> <p>The prostate cancer working group (PCWG) is the generally accepted definition and SPARTAN used that definition and then selected the high risk group. Hence, the results of the SPARTAN trial can be generalized to the PCWG definition.</p>
Intervention	Prior treatments	SPARTAN excluded patients who received prior chemotherapy for prostate cancer, except if administered in the adjuvant/neoadjuvant setting.	Are the results of the trial generalizable to patients who received prior chemotherapy?	<p>The CGP feels that these are reasonable exclusion criteria, based on available evidence. Prior chemotherapy (except in the adjuvant/neoadjuvant setting) was not permitted in the SPARTAN trial and these patients should be excluded from apalutamide treatment. However, the CGP felt that apalutamide would be a reasonable treatment option for patients who received chemotherapy in the adjuvant/neoadjuvant setting.</p>
		The trial also excluded	Are the results of	History of treatment

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
		patients with a history of treatment with second generation anti-androgens (e.g., enzalutamide).	the trial generalizable to patients who received prior treatment with second generation anti-androgens?	with second generation anti-androgens was not permitted in SPARTAN and these patients should be excluded from apalutamide treatment. However, the CGP felt that apalutamide would be a reasonable treatment option for patients who received enzalutamide as part of a clinical trial. Patients should not be disadvantaged for participating in a clinical trial. Hence if they participated in one and received enzalutamide as an experimental treatment they should have access to standard of care, which here would then be apalutamide.
		SPARTAN included patients who already receive a first generation anti-androgen (e.g. bicalutamide, flutamide, nilutamide) if they had at least a 4-week washout prior to randomization AND show continuing disease (PSA) progression (an increase in PSA) after washout. The majority of patients in the SPARTAN trial (in both treatment arms) had already received a combination of ADT and a first generation anti-androgen.	Are the results of the trial generalizable to patients who had already started ADT plus an anti-androgen?	All of these patients had to have been on androgen deprivation therapy either with a LHRH antagonist alone or a LHRH plus an antiandrogen. If they had been on both the antiandrogen was to be stopped and PSA observed. That reflects a clinical standard. Hence it is fully generalizable.
		The majority of patients in the SPARTAN trial (in both treatment arms) had received two or more prior hormonal	Are the results of the trial generalizable to patients who are undergoing secondary	The results are fully generalizable to patients undergoing secondary hormonal manipulation. These secondary hormone

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
		therapies.	hormonal manipulation (e.g., changing bicalutamide to megestrol acetate, or antiandrogen withdrawal)?	maneuvers are part of standard therapy for hormone sensitive disease and can be tried. They are usually not very effective and I would assume that the introduction of apalutamide will decrease the use of these secondary maneuvers.
Comparator	Standard of care	In the SPARTAN trial, Placebo was used as a comparator.	If the comparator is non-standard, are the results of the trial applicable in the Canadian setting?	There is currently no standard of care and no approved regimen for patients with non-metastatic castration resistant prostate cancer in Canada. Placebo is appropriate comparator.
Outcomes	Appropriateness of primary and Secondary Outcomes	SPARTAN measured the following clinical outcomes: Primary- MFS Secondary- time to metastasis (BICR-assessed), PFS(BICR-assessed), time to symptomatic progression, OS, and time to the initiation of cytotoxic chemotherapy	Were the primary and secondary outcomes appropriate for the trial design?	For non-metastatic castration resistant prostate cancer, MFS is a meaningful endpoint for patients because it delays the onset of metastatic disease which is associated with more fatigue, pain, less wellbeing and potential bone complications such as fractures and need for radiation. The primary endpoint is supported by secondary outcomes in favour of apalutamide. Especially time to symptomatic progression is an important clinical endpoint for patients, who value living longer without symptoms.
Setting	Trial centres	The trial was conducted in 332 sites in 26 countries, including: Australia (15), Austria (2), Belgium (3), Canada (27), Czech Republic (7), Denmark (4),	Do the trial results apply to patients from Canadian centres? Are there any known differences in practice patterns between the	Overall, most patients were from Canada or the US, where practice patterns are similar to Canada.

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
		Finland (3), France (18), Germany (19), Hungary (1), Israel (6), Italy (10), Japan (22), Netherlands (6), New Zealand (3), Norway (1), Poland (10), Romania (3), Russia (9), Slovakia (3), South Korea (11), Spain (27), Sweden (5), Taiwan (6), United Kingdom (15), United States of America (96)	countries listed and Canada?	
	Trial centres	Manufacturer did not confirm whether the participating sites(n=332) were academic centres or community treatment centres	If the trial was conducted only in academic centres are the results applicable in the community setting?	It is likely that apalutamide will be handled across different practice settings in Canada (e.g. by radiologists or radiation oncologists, academic versus community setting etc.). The CGP feels that it is not necessary to restrict the use of apalutamide to certain practitioners and practices as differences in practice pattern would likely not affect treatment effect of apalutamide and similar drugs (i.e. enzalutamide and abiraterone) are already used routinely and successfully across different practice settings.
	Practice setting	Professional backgrounds of care-providers who were in charge of treating patients are unknown.	Is the type of practice an effect modifier? Do the trial results apply to all practice settings in Canada?	
ADT = Androgen Deprivation Therapy; BICR= blinded independent central review; ECOG = Eastern Cooperative Oncology Group; MFS = metastasis-free survival; OS = Overall survival; PFS = progression-free survival; PSA = prostate-specific antigen; PSADT= prostate-specific antigen doubling time				

1.2.4 Interpretation

Burden of Illness and Need

Non-metastatic castration-resistant prostate cancer (nmCRPC) is a state defined by serum testosterone <3 nmol/L and rising prostate-specific antigen (PSA) and no evidence of metastatic disease. In Canada, the number of new prostate cancer cases in 2017 and expected death rate of nmCRPC have been estimated as approximately 22,000 men/year and 4,000-4,500 men, respectively, with a 34% annual progression to metastatic castration-resistant prostate cancer (mCRPC) and overall mortality of 16%.⁵ It therefore represents a significant patient group with a high risk for progression to metastatic disease.

No single standard-of-care treatment exists for nmCRPC. All previous phase 3 trials of denosumab, zoledronic acid, atrasentan, zibotentan, and clodronic acid failed to show an overall survival (OS) benefit in this population.⁶⁻¹⁰ Many men experience a relatively indolent disease course. For many patients including those with high risk features, generally defined by a shorter PSA doubling time (<8-10 months) and higher baseline PSA, secondary hormone therapies such as the first-generation antiandrogen bicalutamide, ketoconazole, corticosteroids, or estrogens have been utilized with sparse data to support their use.¹¹

Patients with nmCRPC were specifically excluded from both the COU-AA-302 study (abiraterone/prednisone for chemotherapy-naïve metastatic CRPC) and the PREVAIL study (enzalutamide for chemotherapy-naïve metastatic CRPC).^{12,13} Consequently, the optimal management of nmCRPC remains an unmet need for a large number of patients.

The CGP would like to address a statement provided by one of the registered clinicians providing input to this submission. In the clinician input it was stated that apalutamide is a 'nice to have' therapy but is not a necessity referring to results of the STAMPEDE trial. The CGP assume that the comment "nice to have" refers to the lack of a yet proven overall survival benefit. Overall survival is considered the "ultimate" endpoint whereas metastases-free survival is considered by some experts a "relative" important endpoint. Ideally, early treatment with apalutamide would result in an overall survival benefit. To date the results for overall survival in the SPARTAN trial are not mature, however, the interim analysis has demonstrated a very promising trend for overall survival. It would be "nice to have" apalutamide because of the benefits of metastasis-free survival which have been summarized by the CGP in this interpretation and conclusion. There was a reference to the STAMPEDE trial, however, the CGP is not aware of any data regarding this group of patients with non-metastatic CRPC from the STAMPEDE trial.

Effectiveness

The SPARTAN trial is a randomized controlled trial evaluating apalutamide in nmCRPC. Patients deemed to be at high risk for development of metastatic disease were randomized in a 2:1 ratio to receive either apalutamide or placebo.¹ Placebo represents an appropriate comparator for this clinical scenario since no drug has yet demonstrated a benefit for these patients. Main inclusion criteria were appropriate and consisted of men with castrate resistant disease with high risk features, defined as a PSA doubling time of ≤ 10 months during continuous androgen deprivation therapy (ADT). All patients had negative baseline bone scan and CT scans of the head/chest/abdomen/pelvis which are the standard imaging methods used in clinical practice to rule out metastases.

Patient characteristics were well balanced between the 2 groups and consistent with the characteristics of patients commonly seen in Canadian clinical practice. Median age was 74 years and 70% of patients had a PSA doubling time of less than 6 months. Only 10% of patients were treated with bone resorption inhibitors. Seventy-two percent of patients had previously failed one and 28% had failed two forms of ADT. In addition, the majority of patients had been recruited in North America (including Canada) or Western Europe which makes the results fully applicable to a Canadian patient population.

Importantly, the primary endpoint of this study was metastasis-free survival and overall survival was a secondary endpoint. The transition from non-metastatic CRPC to detectable metastatic disease is a clinically relevant event and often heralds the onset of pain, fatigue, weakness and a decline in overall quality of life. Furthermore, the development of metastatic disease frequently leads to the introduction of additional interventions.

Metastasis-free survival is a reasonable end point; however, in order to ensure that sufficient clinical benefit will be realized, an agent would also require a substantial magnitude of improvement to lead to favourable balance in the benefit-risk for toxicity and cost evaluation.

Apalutamide demonstrated a substantive benefit by demonstrating an increase in metastasis-free survival from 16.2 to 40.5 months for the placebo and apalutamide groups, respectively. This was both highly statistically significant (HR for metastasis or death 0.28, 95% CI 0.23-0.35, $p < 0.001$) and clinically meaningful.

In addition, important secondary endpoints were also positive. Time to symptomatic progression was significantly longer for apalutamide compared to placebo (HR of 0.45 [95% CI: 0.32-0.93], $p < 0.01$.) Median time to metastasis [HR 0.27, 95% CI 0.22-0.34], median time to cytotoxic chemotherapy [HR 0.44 95% CI: 0.29-0.66] and median progression free survival [HR 0.29 95% CI: 0.24-0.36] were significantly prolonged and considered to be clinically meaningful.

Overall survival is immature at present and longer follow-up time is required to determine the magnitude of potential benefit. Nevertheless, there is a favourable OS trend for apalutamide [HR 0.70, 95% CI 0.47-1.04].

Although the SPARTAN trial was not designed to formally evaluate sequential treatment, the trial provides valuable evidence about subsequent therapies. 74% of patients in the placebo group subsequently received therapy for metastatic disease with abiraterone/prednisone. Despite the high rates of subsequent therapy, the exploratory endpoint secondary progression-free survival (defined as the time from randomization to investigator-assessed disease progression during first subsequent treatment for metastatic CRPC) favoured apalutamide [HR 0.49, 95% CI: 0.36-0.66] and is suggestive that earlier treatment appears to be better than treatment at the onset of metastases.

Safety

Apalutamide was well tolerated. Even though the apalutamide group had a longer median duration (16.9 months in the apalutamide arm and 11.2 months in the placebo arm) of use, the incidence and severity of adverse reactions were similar to those in the placebo group. Serious adverse events occurred in 25% and 23% of patients, respectively; grade 3 to 4 adverse events were observed in 45% and 34%, respectively. Most common grade 1 or 2 side effects included fatigue, hypertension, rash, diarrhea, nausea weight loss, arthralgias and falls. Similar to enzalutamide, a very small number of patients (0.2%) suffered a seizure during treatment with apalutamide. Apalutamide should therefore be cautioned in patients with a history of seizures and/or are on drugs which can lower the seizure threshold. An increased fracture risk (12% in the Apalutamide arm versus 6.5% in the placebo arm) was observed with the use of apalutamide. Increased osteopenia is a known side effect of antiandrogen therapy and has similarly been observed with all second generation hormonal agents. This can potentially be ameliorated with the use of bone conserving therapies such as calcium, vitamin D, bisphosphonates, and/or denosumab. The favourable toxicity profile of apalutamide was further supported by an exploratory analysis of patient-reported outcomes data, which revealed no notable adverse signals in symptom or functional effects despite the long treatment duration. The tolerability of apalutamide in the SPARTAN trial mirrors the previous experience with this class of drugs in the metastatic castration resistant setting e.g. enzalutamide.

No predictive biomarker is available which would allow the proper selection of patients for apalutamide.

Several questions have been raised regarding the generalization and applicability of these results to certain patient populations:

The trial limited inclusion to patients with ECOG performance status 0 and 1. The majority of patients are in good performance status and are relatively free of symptoms at baseline and this would be fully expected given the absence of metastatic disease using conventional imaging modalities. Those patients with worse baseline performance status likely had existing comorbidities which affect performance status rather than the prostate cancer itself. Indeed, concurrent comorbidities are common in the age group of men who develop prostate cancer. Therefore, reduced performance status should not be a criterion to exclude patients from apalutamide treatment.

The trial included only high risk patients. It is currently unclear whether these results are applicable to patients without the high risk features as defined in the SPARTAN trial (i.e. PSAD_t ≤ 10 months). Patients with lower risk features (i.e. PSAD > 10 months) generally have a longer natural history and the time to metastatic disease is substantially longer. The risk for toxicity/cost/benefit ratio would need to be determined in a clinical trial for these low risk patients. The currently available data do not allow a clear recommendation for low risk patients.

The trial used placebo as comparator. Since there is no defined and generally accepted or approved standard therapy for patients with high risk non-metastatic prostate cancer and none of the drugs tested to date have demonstrated a meaningful benefit, placebo is the appropriate comparator.

Appropriate treatment for metastatic disease after treatment with apalutamide in the non-metastatic setting. CGP notes that there is not sufficient data to make an evidence based recommendation and therefore the following statements are based on expert opinion only and conclusions drawn from similar clinical scenarios. Treatment options after failure of apalutamide include docetaxel, cabazitaxel, radium-223 and abiraterone/prednisone. Since apalutamide is in the same class of drugs as enzalutamide sequential treatment with both drugs does not seem promising. Whether re-challenging with enzalutamide is potentially reasonable after interim treatment with other options is currently unknown. The data available to date for the sequence of enzalutamide followed by abiraterone/prednisone demonstrate a very modest benefit for this sequence.

Enzalutamide followed by Apalutamide for patients who have been treated with abiraterone, enzalutamide or other second generation anti-androgens through a clinical trial or private drug insurance. This sequence has the same shortcomings as the sequence discussed above, of apalutamide followed by enzalutamide. The CGP would not consider that sequence as a standard in practice. There is no data at the moment for the sequence of abiraterone/prednisone followed by apalutamide. Data for the sequencing of abiraterone/prednisone followed by enzalutamide in the metastatic CRPC setting demonstrate a modest benefit. From a clinical trial perspective and the most important trials paradigm that patients are not to suffer any disadvantages, the CGP thinks that clinical trials patients should be permitted to receive apalutamide should the treating physician consider this appropriate.

1.3 Conclusions

The Clinical Guidance Panel concluded that there is a net overall clinical benefit to apalutamide for high-risk non-metastatic castration resistant prostate cancer patient based on one high-quality randomized controlled trial that demonstrated a statistically significant and clinically meaningful benefit in metastasis-free survival and almost all secondary endpoints including progression-free

survival, time to symptomatic progression, and time to cytotoxic chemotherapy for apalutamide compared with placebo. Overall survival is currently immature but demonstrates a positive trend in favour of apalutamide. Exploratory endpoints, including second progression-free survival, also favoured the use of apalutamide and indicate a benefit for earlier rather than later treatment. Treatment was well tolerated with few clinically relevant grade 3 and 4 side effects and this was supported by patient reported outcomes. No treatment options exist for patients with non-metastatic castration resistant prostate cancer. Hence there is an urgent need for effective treatment options in this patient population.

This recommendation was based on the SPARTAN trial which evaluated the use of apalutamide in high-risk non-metastatic castration resistant prostate cancer.

Based on previous experience with this patient population and with similar agents in the castration-resistant metastatic setting, the excellent tolerability of apalutamide and the high unmet need for these patients, it would be reasonable to expand apalutamide to patients with a good/acceptable performance status (ECOG 0-2).

In making this recommendation, the Clinical Guidance Panel considered:

- The transition from non-metastatic CRPC to detectable metastatic CRPC is a clinically relevant event and often associated with the onset of pain, fatigue, weakness, decline in overall quality of life, psychological burden and additional interventions.
- While significant advances have been achieved in recent years in the treatment of castration resistant prostate cancer, it remains an incurable disease. A significant portion of patients with prostate cancer will eventually relapse and progress to overt metastatic disease which is associated with a high burden of symptoms, decrease in quality of life and death.
- The Spartan trial demonstrates a statistically significant as well as clinically meaningful benefit for these patients as described above.
- Apalutamide was well tolerated in this patient population.
- No data exist for low risk patients with a PSA doubling time of < 10 months and it is uncertain whether the benefit observed in SPARTAN extends to this patient population.
- The identification of non-metastatic patients in SPARTAN was based principally on PSA and conventional imaging modalities of bone scan and CT. Advanced imaging techniques currently in development (e.g. PET scans) may have an ability to detect metastases earlier than current imaging techniques. As a result more patients may be identified with evidence of early metastatic disease. The impact of treatments in this future cohort of patients has yet to be determined.

2 BACKGROUND CLINICAL INFORMATION

This section was prepared by the pCODR Genitourinary Clinical Guidance Panel. It is not based on a systematic review of the relevant literature.

2.1 Description of the Condition

Prostate cancer is the most common cancer diagnosed in Canadian men (excluding non-melanoma skin cancers), and is the third leading cause of cancer related death with 4,100 deaths expected in 2017.⁵

2.2 Accepted Clinical Practice

Treatment for Localized Prostate Cancer and Hormone-sensitive Metastatic Prostate Cancer:

Treatment options for localized prostate cancer include prostatectomy, radiation therapy (intensity modulated radiation therapy or brachytherapy) or active surveillance for patients with lower risk disease. There is no definitive evidence that one treatment modality is superior in efficacy. However, despite local ablative treatment, a number of patients develop recurrent disease as evidenced by a biochemical recurrence (elevation in PSA) with or without metastases. Aside from salvage local therapies, such as salvage radiation therapy after previous prostatectomy or salvage prostatectomy after previous radiation therapy, standard first-line therapy for recurrence remains androgen deprivation therapy. The majority of patients initially respond to androgen deprivation therapy but almost all eventually progress to castration resistant prostate cancer (CRPC).

Treatment for Hormone-sensitive Metastatic Prostate Cancer:

The mainstay of standard first-line therapy for metastatic hormone-sensitive prostate cancer remains androgen deprivation therapy either with a LHRH antagonist or agonist, peripheral antiandrogens, bilateral orchiectomy or a combination of LHRH inhibition or bilateral orchiectomy combined with a peripheral antiandrogen. All patients in SPARTAN were treated with one of these options. However, recently two studies have demonstrated additional benefit for the addition of either 6 cycles of docetaxel or the addition of abiraterone/prednisone in metastatic castration-sensitive patients with high risk features. Both treatment options are now considered standard of care in their respective patient populations.

In the CHARTED study high-volume disease was defined as presence of visceral metastases and/or \geq four bone metastases with at least one outside of the vertebral column and pelvis in this study. A significant overall survival benefit was observed for patients treated with androgen deprivation therapy and 6 cycles of docetaxel.¹⁴

In the LATITUDE study high risk was defined as positive bone scan or metastatic lesions at the time of diagnosis on computed tomography (CT) or magnetic resonance imaging (MRI), according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. In addition, the patients were required to have at least two of the three following high-risk factors associated with poor prognosis: a Gleason score of 8 or more (on a scale of 2 to 10, with higher scores indicating more aggressive disease), at least three bone lesions, and the presence of measurable visceral metastasis. Abiraterone/prednisone in combination with androgen deprivation therapy significantly prolonged overall survival and has now been recognized as a standard management option for patients with high risk castration-sensitive disease.¹⁵

The majority of patients initially respond to androgen deprivation therapy ± docetaxel or abiraterone/prednisone but almost all eventually progress to castration resistant prostate cancer (CRPC).

Treatment for Asymptomatic Non-metastatic CRPC:

CRPC is defined as disease progression in the setting of castrate testosterone levels.^{16,17} Biochemical progression as manifested by a rising PSA alone is often the initial sign of disease progression before developing metastatic disease to bone or visceral organs. No accepted standard treatment options have been defined for patients with non-metastatic castration-resistant prostate cancer as no phase 3 study has yet demonstrated improved overall survival or these patients were not included in trials for castration-resistant prostate cancer. In the absence of proven treatment options, observation is often recommended for patients with biochemical-only progression and no evidence of metastases. Alternatively, initial therapy with the addition of an anti-androgen such as bicalutamide or an androgen synthesis inhibitor such as ketoconazole can be used although no secondary hormonal therapy has been found to extend survival for patients with CRPC. If patients are treated with combined androgen blockade, anti-androgen withdrawal as well as low dose prednisone are considered further options. In general, early chemotherapy with docetaxel is not recommended for those patients without metastatic disease outside the context of a clinical trial. Importantly, patients with non-metastatic CRPC were not included in the COU-AA-302 study (abiraterone/prednisone for chemotherapy-naïve metastatic CRPC) or the PREVAIL (enzalutamide for chemotherapy-naïve metastatic CRPC) and hence their treatment remains an unmet need.^{12,18}

Treatment for Minimally Symptomatic and Symptomatic CRPC:

For those with mCRPC who are asymptomatic or minimally symptomatic, secondary hormonal maneuvers with abiraterone/prednisone, an androgen synthesis inhibitor, or enzalutamide, an androgen receptor antagonist, are often utilized. Both drugs have demonstrated a statistically significant and clinically meaningful overall survival benefit compared to placebo/prednisone or placebo alone within randomized phase III studies and have become the most frequently used standard of care in first-line treatment for metastatic CRPC. Alternatively, docetaxel chemotherapy can be considered in patients with good performance status.

When secondary hormonal therapies fail, suitable patients are treated with docetaxel chemotherapy. A large randomized phase 3 study docetaxel significantly improved overall survival by over 2 months, was associated with a PSA response rate of approximately 50% and also improved quality of life.¹⁹ Docetaxel was approved by Health Canada in 2004 for the treatment of mCRPC. Although effective, docetaxel is a palliative treatment and eventually all patients develop progressive disease.

Radium-223 is an alpha-emitting radiopharmaceutical which has been approved by Health Canada in 2013 for treatment of symptomatic bone metastasis in patients with CRPC with no visceral metastasis based on a modest survival advantage over placebo (14.9 vs 11.3 months, HR 0.70, 0.58-0.83, P<0.001).²⁰ Radium-223 can be indicated for patients who are initially treated with chemotherapy, or alternatively, hormonal therapies such as enzalutamide and abiraterone.

Cabazitaxel, a novel semi-synthetic taxane was shown to increase overall survival as well as response rates and time progression when compared to mitoxantrone in the post docetaxel setting.²¹

Both enzalutamide and abiraterone acetate were compared to placebo and prednisone after docetaxel chemotherapy, respectively within phase III studies and were found to be associated with improved overall survival.^{22,23}

Importantly the post chemotherapy enzalutamide trial (AFFIRM trial)²³ did not include patients treated with abiraterone prior to docetaxel and neither did the post-chemotherapy abiraterone/prednisone trial (COU-AA-301 trial)²² include patients treated previously with enzalutamide, so the optimal sequencing of these new therapies remains undefined. Furthermore, the repeat use of abiraterone or enzalutamide in the post chemotherapy setting in patients previously exposed to abiraterone or enzalutamide in the minimally symptomatic setting is undefined.

Expected place of Apalutamide in the treatment algorithm of CRPC:

Patients with non-metastatic castration resistant prostate cancer (nmCRPC) are at risk of progressing to metastatic disease imminently within 1 to 2 years.^{11,24} The onset of metastases is usually accompanied by a decreased quality of life, increased symptoms such as pain, weight loss, loss of appetite etc., and a limited life expectancy.²⁵⁻²⁸ Overall survival of patients with metastatic disease is approximately 2.5 years. As mentioned above, no standard therapy option exists for patients with non-metastatic castration resistant prostate cancer. These patients had been excluded from the pre-chemotherapy enzalutamide (PREVAIL study)¹², the abiraterone/prednisone trial (COU-AA- 302 study)¹³ and the docetaxel in metastatic castration-resistant prostate cancer study (TAX-327 trial)¹⁹.

Management options are very limited and include watch and wait, secondary hormone maneuvers or low dose prednisone, all of which have a very modest, if at all effect on outcomes.

Recently, enzalutamide has been reported to be beneficial in non-metastatic castration-resistant patients, however the final overall survival analysis is pending (PROSPER study).²⁸ If positive, enzalutamide may become a treatment option in this patient population as well. Apalutamide has been tested in this space within the randomized, double-blind, placebo-controlled phase III SPARTAN trial comparing apalutamide + ADT vs. placebo + ADT, in patients with non-metastatic castration-resistant prostate cancer.¹

Apalutamide is an oral, next-generation androgen receptor inhibitor. Apalutamide binds directly to the ligand-binding domain of the androgen receptor and prevents androgen-receptor translocation, DNA binding, and androgen-receptor-mediated transcription. The SPARTAN study demonstrated substantial clinical benefit for treatment with apalutamide + ADT through statistically significant and clinically meaningful improvements in metastasis-free survival (MFS) and time to symptomatic progression, and potential improvement in overall survival based on positive survival trend.

2.3 Evidence-Based Considerations for a Funding Population

The currently available evidence supports the use of apalutamide for patients with non-metastatic castration-resistant prostate cancer.

Patients with nmCRPC are characterized by an observed rising PSA despite androgen-deprivation therapy and castrate testosterone levels as well as no detectable bone or soft tissue distant metastases on imaging.

Currently, no clinically useful and reliable biomarkers exist for the prediction of response and/or benefit.

2.4 Other Patient Populations in Whom the Drug May Be Used

No evidence exist for the use of apalutamide in the following therapeutic situations:
Castration-sensitive metastatic prostate cancer

Castration-resistant metastatic prostate cancer (prior or post chemotherapy)

Apalutamide has not been approved for any other indication than prostate cancer.

3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

Three patient advocacy groups, PROSTAID Calgary, the Canadian Cancer Survivor Network (CCSN), and the Prostate Cancer Centre (PCC), provided input on the apalutamide (Erleada) submission for the treatment of non-metastatic castration resistant prostate cancer (nmCRPC).

PROSTAID Calgary conducted a survey using Survey Monkey titled, “PROSTAID Calgary Disease State and Medication Survey”. A total of 165 respondents completed the survey. Available demographic data from the respondents indicate that 96 individuals were from Alberta, two were from Saskatchewan, seven were from British Columbia, and three were from Ontario. The majority (n=118) of respondents were prostate cancer survivors, 33 were survivors of prostate cancer whose prostate cancer had recurred, and 14 were caregivers of men with prostate cancer. Only one patient reported having experience with apalutamide.

CCSN also conducted a survey using Survey Monkey. CCSN’s survey was conducted in April 2018, and was advertised on their website (survivor.net), their Facebook and Twitter social media pages, and in their April e-letter (<https://mailchi.mp/survivornet.ca/ccsn-april-e-letter-999641>). CCSN circulated their survey through email to approximately 125 prostate cancer support groups and to CCSN’s Prostate Cancer Advisory Council. The survey conducted by CCSN was completed by 34 respondents, 29 patients and five caregivers. One patient reported having experience with apalutamide. Demographic data about respondents were not available in the patient input submitted by CCSN.

PCC conducted a survey among participants who were part of clinical trials at the centre. PCC distributed their survey either directly to the patient or by mail or e-mail; in one case the survey was administered via telephone. There were a total of 24 respondents, 21 of whom were patients while three were caregivers. All participants were Caucasian and from Alberta, except one patient who was from British Columbia but had travelled to Alberta for his prostate cancer. The majority of respondents were over 60 years of age (13 respondents in 61-70 years age group, and 8 in 71-80 years age group). Two respondents were between 51 and 60, and one was between 81 and 90 years of age. Five respondents had experience with apalutamide; four respondents were being treated with a different drug for the same indication as apalutamide, either placebo or ODM-21, a non-steroidal AR inhibitor through the ARAMIS trial; 15 respondents had high risk non-metastatic hormone sensitive prostate cancer and were receiving androgen deprivation therapy, but were included in the survey as they were at risk of progressing to castration resistant prostate cancer and it was decided that these respondents would benefit from apalutamide in the future.

In total, 201 patients and 22 caregivers completed the surveys (Table 1).

Table 1: Summary of Survey Respondents

	Patients	Caregivers	Experience with Apalutamide
PROSTAID Calgary	151	14	1
CCSN	29	5	1
PCC	21	3	5
Total	201	22	7

From a patient's perspective, there were a number of negative sentiments about patient's experiences with prostate cancer. The following issues were perceived by the survey participants to have a negative impact on quality of life: challenges with intimacy and sexual dysfunction, patients' negative psychological feelings regarding their "manhood", and urinary incontinence.

There were a number of quotes from PROSTAID Calgary asserting feelings that physicians are biased towards surgical treatment options, and that patients are not given opportunities to consider alternative treatment methods. The survey results suggested that patients felt strongly about being given treatment options other than surgery.

In terms of expectations for alternative treatment options, focus was placed on improving quality of life and managing or reducing side effects. Patients reported feeling anxious about whether they will qualify for further treatment, and worry about how prostate cancer will affect their future.

In total, seven respondents indicated having experience with apalutamide. Two patients did not experience any side effects related to apalutamide, and the remaining five reported minimal, only one or two, side effects, including hot flashes, reduced bone density, lowered PSA levels, and increased fatigue. Relative to the experienced side effects, participants had an overall positive attitude toward apalutamide; the benefits of the drug were considered to outweigh the risk of the side effects.

Please see below for a summary of specific input from PROSTAID Calgary, CCSN and PCC. Quotes are reproduced as they appeared in the surveys, with no modifications made for spelling, punctuation or grammar. The statistical data that were reported have also been reproduced according to the submission and have not been corrected.

3.1 Condition and Current Therapy Information

3.1.1 Experiences Patients have with [Castration Resistant] Prostate Cancer

According to PROSTAID Calgary, CCSN and PCC respondents reported a variety of negative emotions associated with having prostate cancer. Over half of individuals responding to PROSTAID Calgary's survey (55%) reported suffering with issues of intimacy, 30% reported feelings of worry and anxiety, and over 25% reported negative psychological feelings toward their 'manhood'. A direct connection was made by respondents between their loss of erection and intimacy. Depression, incontinence and impotence were most commented on by patients. Some patients even reported divorce as an unfortunate outcome of their prostate cancer diagnosis, with depression and fatigue being the most commonly referred to underlying causes. However, patients reported a better quality of life, when their partners or caregivers were understanding and compassionate.

"Prostate cancer takes a lot away from just about everything which was heretofore considered normal. In terms of intimacy, one has to accept enormous change and adjust to it. When one is fortunate enough to have a loving and understanding wife everything is made easier."

CCSN also reported that symptoms affecting patient's day-to-day living and quality of life as being the most important to patients. Sexual dysfunction, fatigue, and urinary incontinence were reported by over half of respondents to CCSN's survey (Table 2). Similar to respondents of PROSTAID Calgary's survey, respondents of CCSN's survey reported feelings of anxiety, worry and uncertainty. Patients also added feelings of "mild depression right after treatment",

“stress incontinence”, and “having hot flashes” as being problems experienced due to their condition.

Table 2: Symptoms Most Affecting Patient’s Daily Living and Quality of Life

Symptom	%
Sexual dysfunction	76%
Fatigue	55%
Urinary incontinence	55%
Living with uncertainty	41%
Not sleeping at night (restlessness)	32%
Anxiety, panic attacks	17%
Pain	15%
Feelings of isolation or loneliness	12%
Weight loss, lack of appetite	3%

CCSN asked symptoms control. Over incontinence, being the important for

Table 3: Symptoms Patients Consider Most Important to Control

Symptom	%
Urinary incontinence	58%
Sexual dysfunction	52%
Fatigue	52%
Living with uncertainty	30%
Not sleeping at night (restlessness)	27%
Pain	15%
Anxiety, panic attacks	12%
Feelings of isolation or loneliness	6%
Weight loss, lack of appetite	0%

patients to rate their top three that were the most important to half of respondents stated urinary sexual dysfunction and fatigue as symptoms they considered most them to control (Table 3).

Respondents from both PROSTAID Calgary and CCSN surveys indicated negative impacts of prostate cancer on their daily living and quality of life. Mainly, patients were concerned with issues related to intimacy, sexual dysfunction, incontinence, and anxiety.

Among the respondents of PCC's survey, 70% reported being negatively impacted by prostate cancer in their daily lives, while the remaining 30% reported no or minimal impact. PCC noted that among the 70% of respondents who reported being negatively impacted by prostate cancer, all had a prostatectomy or cryosurgery for curative intent. Similar to respondents from surveys distributed by PROSTAID Calgary and CCSN, the majority of respondents of PCC's survey indicated stress about their sexual dysfunction and incontinence. Approximately 30% of respondents also reported having difficulty with their relationships with their partners due to prostate cancer. Poor energy levels and hot flashes were other commonly reported side effects due to treatments, resulting in decreased travel plans and activity levels. More than half of respondents also reported concerns about their future, or "*what comes next*". Approximately 20% of PCC's respondents indicated financial impacts; for example, having to reduce their working hours or stop working altogether, changing spending habits, or giving up personal hobbies. The following quotes were provided by PCC:

- *"I had to eventually give up some sports, skiing, golfing, and extended travel. Have had to cut back on some of my volunteering."*
- *"I would have been able to work longer thereby increasing my pension income"*
- *"I retired 20 years ago so a lot of adjustments had to be made with respect to income."*
- *"It is stressful to think about my husband's prostate cancer so it is impacting my business because I want to spend more time with him, less time at work."*

3.1.2 Patients' Experiences with Current Therapy for Castration Resistant Prostate Cancer

Side effects reported by PROSTAID Calgary were hot flashes, sleep disturbances incontinence, lack of bowel movement control, depression, difficulty urinating, erectile dysfunction (ED), extreme headaches and nasal congestion, weight gain, and breast enlargement.

PROSTAID Calgary mentioned 'dissatisfaction with doctors' as a commonly occurring theme among respondents. Mainly, PROSTAID Calgary suggested that there was dissatisfaction regarding the lack of options provided to patients before surgeons operated. It was suggested that surgeons choose to operate before presenting or exploring alternative options. The following quotes were provided by PROSTAID Calgary:

- *"Very little information regarding changing your nutritional habits in helping with watchful waiting. Plus the doctors I saw in my journey were very territorial.... We were on our own. Hard to believe BUT some doctors were saying things that were not true. IMO, the surgeons who wanted to operate using their hands appeared close minded ... lots more but will leave it at that!"*
- *"Yes proper treatment for incontinence and ED and depression is very difficult to access and have not received proper treatment."*
- *"Doctor lacks of knowledge to heal without surgery and measure risk, always said you must go for a surgery because your PSA will go up in 6 months or a year. So far I have 6 years with a stable PSA. Doctor scare you more than help me. They don't want to search for another choices or learn new options."*

CCSN survey participants reported radiation therapy, hormone therapy (including Zoladex, Firmagon, Prolia, and Lupron), immunotherapy, and surgery as the treatments patients were most using (Figure 1). Other treatments included antiandrogen medications, chemotherapy, and steroids. CCSN reported that 10% of patients were clinical trial participants; however, the type of the trial treatment was not specified.

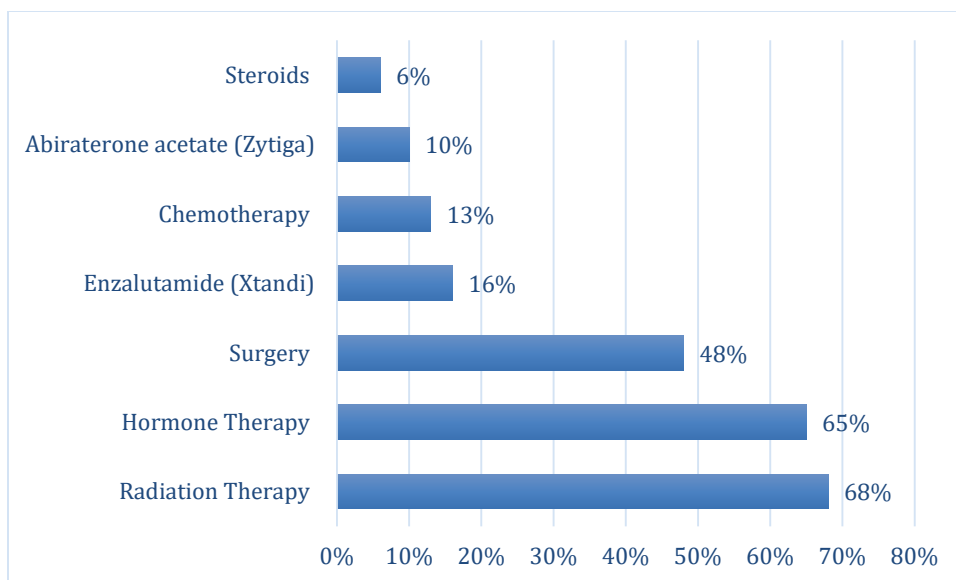


Figure 1: Patient Treatments

The most frequent side effects treatments patients were using included diarrhea (23%), nausea/vomiting (5%), and risk of infection (5%). Other reported side effects included: constipation, urinary incontinence, hot flashes, joint pain, and fatigue. According to CCSN, over half of respondents (57%) did not have issues accessing treatment, while 15% of them did. Respondents also provided reasons for their limited accessibility of treatment including limited availability in their community, travel costs, and issues with administration. CCSN noted that some respondents indicated multiple issues related to accessibility of treatment, and that some respondents also chose not to answer.

PCC indicated that all respondents considered having available treatments that would allow them to remain metastasis free were important to them. Quotes provided by PCC indicate feelings of fear and anxiety about the future, progression of disease, and about finances:

- *“The stress on doing nothing means that 100% I would not survive 10 years”*
- *“It would be the best hope besides a cure”*
- *“it means the world to me to know that I can take a medication that can suppress or delay disease spreading”*
- *“Any aid to slowing the progress of the disease is of paramount importance”*
- *“fear of not being able to afford, should not be turned away due to finances”*

PCC reported some respondents expressed anxiety about whether they could afford necessary treatments. Private health insurance was not present among 40% of respondents, or it was reported that health insurance was only available between the ages of 65 and 70.

Need for Improved Outcomes

PROSTAID Calgary mentioned quality of life and side effects as being the biggest concerns among respondents. PROSTAID Calgary also provided a series of quotes from patients indicating a desire for treatment options other than surgery, treatments with minimal, or manageable, side effects, and anxiety about treatment options that result in only temporary changes. The following quotes were provided:

- *“Every year delay means 1 more year advancement in treatment options and 1 more year closer to finding a cure.”*

- *“Not much, I want another 35 years.”*
- *“That would be great, depending on the side effects.”*
- *“Depends on the treatment. Knowing that I have cancer that eventually will need to be addressed would likely cause some stress if the treatment was only temporary.”*
- *“When I was told that I had prostate cancer and that surgery was an option, I opted for the radical prostatectomy surgery. I was not offered a treatment that could delay progression.”*

When asked about whether current therapies were meeting patient’s needs, 45% of respondents of CCSN’s survey stated that their needs were not being met. The following quotes were provided by CCSN:

- *“PSA has doubled in less than a year three times during five years of of the cancer.”*
- *“I am concerned that more aggressive treatments like abiraterone, enzalutimide, docetaxel, etc. are not be available to me until metastases have spread beyond local lymph nodes and surrounding abdominal tissues.”*
- *“Experimental and pilots are not well advertised.”*
- *“My PSA levels are on the rise again but I am not eligible for further treatment options.”*

Patients responding to CCSN’s survey reported Similar to respondents of PROSTAID Calgary’s survey, CCSN also reported quality of life as being the most requested aspect of life that patients wanted addressed from a new drug (Figure 2). CCSN posits that in order to face the uncertainty about the future and the disease progression, patients are willing to tolerate significant side effects; patients reported being willing to cope with some side effects from new treatments including:

- *“being tired, moderate washroom use instead of every hour.’*
- *“Hot flashes”*
- *“Fatigue, loss of sexual function.”*
- *“hair loss, sexual dysfunction, tiredness”*
- *Almost any if the cancer were to go back into remission.”*

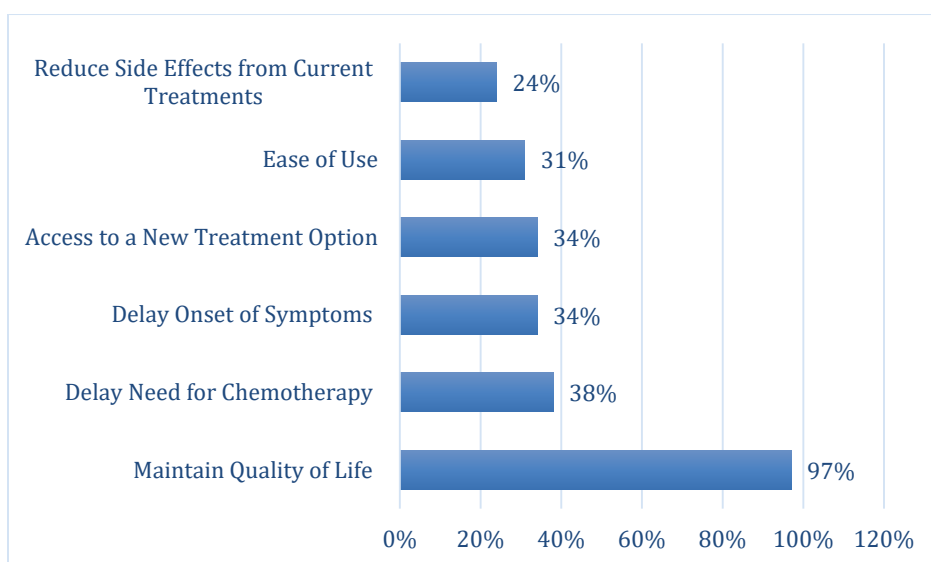


Figure 2: Most Requested Aspects of Living to be Addressed by a New Drug

Using an open-ended question, PCC surveyed respondents about potential outcomes that they thought should be considered when evaluating new treatments for prostate cancer. PCC stated that nearly all respondents reported quality of life as an important consideration with new treatments. In addition to quality of life, overall survival and delayed progression were also common concerns.

3.1.3 Impact of prostate cancer and Current Therapy on Caregivers

CCSN asked caregivers how prostate cancer had affected their lives, and what challenges they faced because of it. Based on quotes provided by CCSN, there were feelings of worry and helplessness about their loved ones condition and prognosis. There were also concerns about maintaining proper diet for their loved ones, and about the future and being unable to plan ahead long term. The following quotes were provided:

- *“Feeling helpless and worrying about prognosis and advance of cancer.”*
- *“worry about prognosis, feeling helpless, managing side effects”*
- *“Can’t plan ahead for more than a few months. Trying to provide my husband with the proper diet and restrict weight gain has been a constant struggle.”*

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for and Experiences To Date with Apalutamide

PROSTAID Calgary reported one patient was reported to have had experience with apalutamide. PROSTAID Calgary described the patient as being from Alberta, castrate resistant, asymptomatic and experiencing hot flashes as their only side effect. When asked about how prostate cancer had affected his day-to-day living and quality of life, there was an overall negative atmosphere regarding the sentiments expressed. Specifically, there negative psychological feelings towards his “manhood”, decreased self-esteem, and issues surrounding relationships and self-esteem.

When asked about what this patient would like to see in a new treatment that was currently not achieved in treatments, the patient expressed a desire for movement toward non-action. There was sentiment surrounding quality of life, as current treatment options negatively impact quality of life too greatly. The metastatic condition of the patient was unknown.

Only one patient was reported to have experience with apalutamide by CCSN as well. Apparently, this patient accessed apalutamide through a clinical trial. This patient reported a positive experience with apalutamide, experiencing no adverse effects. Apalutamide allowed this patient to better manage symptoms. She stated: *“my numbers are encouraging, people tell me I look great and I’m getting stronger.”*

Five respondents part of the sample reported by PCC had experience with apalutamide, all of whom accessed the drug as part of the SPARTAN randomized controlled trial. None of the five respondents reported any difficulties related to taking the drug. Prior to participation in the SPARTAN Trial, all of the five participants received Leuprorelin (Eligard) therapy, and continued to take this therapy throughout the SPARTAN Trial. One of the five patients reported having no side effects since beginning apalutamide, while one reported a decreased bone density, one reported decreased PSA levels, and two reported increased fatigue. Among the patients who experienced side effects, all expressed the sentiment that the experienced side effects of apalutamide were outweighed by the benefits:

- *“the benefits to me are lower PSA and this gives me hope and therefore well worth the side effects”*
- *“ I am very sleepy but I don’t mind that”*

One of the patients enrolled in the SPARTAN trial was randomized to placebo, however was given apalutamide after unblinding occurred. He stated: *“Answer to my prayers. Perhaps it means I will live long enough to see my grandchildren marry and perhaps see my great grandchildren.”*

PCC also asked the five respondents what situation they thought they would have experienced at the time of the survey, had they not received apalutamide. The following are the patients' responses:

- *“I would be more worried”*
- *“Expect cancer would have spread”*
- *“Expect to be in bad shape”*
- *“Just waiting to die”*
- *“Bed ridden or dead”*

3.3 Additional Information

No additional information was provided by PROSTAID Calgary. PCC added additional information on caregiver responses which has been included above in section 3.1.3.

4 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

The Provincial Advisory Group includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The complete list of PAG members is available on the pCODR website (www.cadth.ca/pcodr). PAG identifies factors that could affect the feasibility of implementing a funding recommendation.

Overall Summary

Input was obtained from all nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation:

Clinical factors:

- Clarity of eligible patient population.
- Appropriate treatments for metastatic, castration resistant disease after apalutamide.

Economic factors:

- Add-on therapy to androgen deprivation therapy.

Please see below for more details.

4.1 Currently Funded Treatments

PAG noted that the current treatment for non-metastatic castration-resistant prostate cancer is androgen deprivation therapy (ADT).

4.2 Eligible Patient Population

PAG is seeking clarity on whether or not the following patients would be eligible for treatment with apalutamide:

- Patients who received adjuvant or neoadjuvant chemotherapy,
- Patients with PSA doubling time greater than 10 months,
- Patients who already started ADT plus an anti-androgen (the trial allowed these patients if there was PSA progression after a four week wash out period)
- Patients who are undergoing secondary hormonal manipulation (e.g., changing bicalutamide to megestrol acetate, or antiandrogen withdrawal).

PAG is seeking guidance on the definition of castration-resistance, as there are different definitions (e.g., prostate cancer working group) which may differ slightly from the SPARTAN trial. For example, in some clinical trials, this has been defined by a serum PSA greater than 2 ng/mL and rising over one month, although some clinicians may initiate a discussion of treatment modification with a patient as soon as the PSA has risen twofold.

PAG noted that there is potential for indication creep to use apalutamide in high risk patients (e.g., Gleason score 8-10, high PSA at diagnosis, etc.) who have not had a PSA progression in the non-metastatic setting.

4.3 Implementation Factors

PAG noted that apalutamide is an oral treatment that can be administered at the patient's home and chemotherapy chair time is not required. However, PAG identified that there may be more frequent clinic visits for monitoring of blood work and side effects compared to ADT alone.

Apalutamide is available in one tablet strength and the dose is four tablets daily. Dose adjustments are made by adjusting the number of tablets and there would be minimal drug wastage.

4.4 Sequencing and Priority of Treatments

PAG is seeking information on the appropriate treatment for metastatic disease after treatment with apalutamide in the non-metastatic setting. Treatments available for castration resistant metastatic disease include abiraterone, enzalutamide and chemotherapy. PAG noted that apalutamide and enzalutamide are the same class of drug and seeking information on the use of enzalutamide in the metastatic, castration resistant setting after apalutamide or whether patients previously treated with apalutamide should be treated with abiraterone or chemotherapy in the castration resistant metastatic setting.

PAG identified that there may be a small number of patients who have been treated with abiraterone, enzalutamide or other second generation anti-androgens (e.g., through a clinical trial or private drug insurance) for non-metastatic castration-resistant prostate cancer. PAG is seeking guidance on the appropriateness of using apalutamide following abiraterone, enzalutamide or other second generation anti-androgens after failure of these drugs in this therapeutic space should these patients continue to remain non-metastatic.

4.5 Companion Diagnostic Testing

None required.

4.6 Additional Information

None provided.

5 SUMMARY OF REGISTERED CLINICIAN INPUT

Six clinician inputs were provided for Apalutamide for the treatment of patients with non-metastatic castration resistant prostate cancer (nmCRPC).

The clinicians providing input all expressed that there is currently no funded standard of care for patients with non-metastatic castration resistant prostate cancer (nmCRPC) and that apalutamide does fill an unmet need. It was noted repeatedly that there is a gap in treatment options for patients in this stage of disease because patients must progress to having metastatic disease before they are eligible to receive most treatment options. In terms of sequencing, it was reported by the clinicians that apalutamide would be used in combination with androgen deprivation therapy (ADT), before a nmCRPC patient has developed metastases. It was noted that by adding apalutamide to the available drug options, it may affect which treatment a patient receives if they become metastatic. There is no diagnostic testing required for this drug.

Please see below for details from the clinician input(s).

5.1 Current Treatment(s) for Castration Resistant Prostate Cancer

The clinicians providing input acknowledged that there is currently no funded standard of care for this particular patient population with nmCRPC. It was noted that the treatment options available to this population are limited to ADT with or without secondary hormonal manipulation such as non-steroidal antiandrogens and corticosteroids, however these treatments generally do not have a meaningful impact on clinical outcomes such as delayed progression or improved survival. It was noted by a clinician that patients with nmCRPC may be progressing (locally and biochemically) while on ADT without showing overt signs of metastasis. However, until they have radiographic evidence of metastasis, there are no approved treatment options for these patients. One clinician stated that there was an unmet need in terms of high risk nmCRPC patients, as they are at very high risk for developing symptomatic metastatic disease or dying without treatment.

5.2 Eligible Patient Population

The clinicians providing input reported that, if approved and funded, apalutamide would be prescribed to the patient population reflected in the SPARTAN trial; i.e., castration resistant prostate cancer patients with no metastases (nmCRPC) who are at high risk of developing metastases, with a PSA doubling time of 10 months or less. One clinician added that ideal patient population would be those with nmCRPC, as assessed by rising prostate-specific antigen (PSA \geq 2), and a testosterone level of less than 1.7 nmol/L. It was noted that the inclusion and exclusion criteria and threshold values specified in the SPARTAN trial could be applied in clinical practice easily. One clinician noted that nmCRPC is a relatively smaller patient population compared to metastatic castration resistant prostate cancer (m-CRPC), but still represents a significant group of prostate cancer patients.

5.3 Relevance to Clinical Practice

The majority of clinicians providing input reported that apalutamide is an important treatment option to have because it would fill an unmet need in the specified patient population. It was noted that this treatment has a favourable toxicity profile and is safe, and would be easily tolerated in most patients. The clinicians providing input made note that although the pivotal clinical trial (SPARTAN) did not demonstrate an overall survival benefit, the primary endpoint, delay in metastasis-free survival as well as secondary endpoints (delay in symptomatic progression, delay in progression-free survival with

second therapy) are all clinically meaningful outcomes. Overall, clinicians felt that having a treatment option to patients with nmCRPC is beneficial for disease control and quality of life. Clinicians reported that it is a very frustrating situation for patients and clinicians to be in, where patients fear progression and metastases. Apalutamide will allow clinicians to start therapy in the non-metastatic CRPC setting rather than waiting until the development of metastases, which is the current clinical practice.

In one clinician input, it was noted that this therapy may be more of a “nice to have” therapy rather than a necessity referring to results from the STAMPEDE trial.

5.4 Sequencing and Priority of Treatments with Apalutamide

The majority of clinicians providing input reported that apalutamide, as an add-on to ongoing ADT, is the only therapeutic option available to nmCRPC patient population. It was also noted that there is currently no drug in this space supported by high-quality evidence. Clinicians providing input proposed using apalutamide after a patient has progressed on ADT but before they are eligible to receive therapies to treat metastatic disease, including abiraterone, enzalutamide, Radium-223 and docetaxel.

In terms of patients who progress after receiving this therapy, there were mixed opinions about the next appropriate step in care. Some clinicians believe that patients who progress to metastatic disease should be treated with established second line hormonal therapies such as abiraterone or enzalutamide, or systemic chemotherapy. Others indicated that apalutamide might take away the use of second generation hormonal therapy as first-line therapy for metastatic prostate cancer. Patient receiving apalutamide may develop cross-resistance, similar to that reported with the current androgen receptor targeted therapies (i.e., abiraterone and enzalutamide). Therefore, if a patient receiving apalutamide for nmCRPC progresses to m-CRPC, it is unlikely that abiraterone or enzalutamide would be beneficial and should likely not be used. It was suggested that in these patients, use of non-AR therapies such as docetaxel, cabazitaxel, and radium-223 would be preferable.

5.5 Companion Diagnostic Testing

The clinicians providing input reported that there is no specific biomarker or diagnostic test for required to use apalutamide.

5.6 Additional Information

None.

6 SYSTEMATIC REVIEW

6.1 Objectives

The objective of this review is to evaluate the effect of apalutamide (ERLEADA) for the treatment of patients with non-metastatic castrate resistant prostate cancer (nmCRPC).

No supplemental questions relevant to this pCODR review and to the Provincial Advisory Group were identified.

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the Clinical Guidance Panel and the pCODR Methods Team. Studies will be chosen for inclusion in the review based on the criteria in Table 6.1. Outcomes considered most relevant to patients, based on input from patient advocacy groups are those in bold. The literature search strategy and detailed methodology used by the pCODR Methods Team will be provided in Appendix A in the Clinical Guidance Report.

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
<p>Published and unpublished RCTs</p> <p>In the absence of RCT data, fully published clinical trials investigating the safety and efficacy of apalutamide for nmCRPC will be included.</p>	<p>Adult men with castration-resistant prostate cancer who have no detectable distant metastases by either CT scan, MRI or technetium-99m bone scan.</p> <p><u>Subgroups:</u></p> <ul style="list-style-type: none"> - Age (<65 years vs. 65 to <75 years vs. ≥75 years) - Baseline ECOG performance status (0-1 vs. ≥2) - Baseline serum PSA level (≤median vs. >median) - Baseline PSA doubling time (>6months vs. ≤6 months) - Use of bone sparing agents (yes vs. no) - Local or regional nodal disease at baseline (N0 vs N1) - Previous prostate cancer treatments (type of treatment) - Race (White vs. Black vs. Asian vs. other) 	<p>ADT + apalutamide [240 mg PO once daily]</p>	<p>ADT ± placebo</p>	<p>Efficacy</p> <p><u>Primary:</u></p> <ul style="list-style-type: none"> • Metastasis-free survival <p><u>Secondary</u></p> <ul style="list-style-type: none"> • Time to metastasis • PFS • Time to symptomatic progression • OS • Time to initiation of cytotoxic chemotherapy • Time to PSA progression • PSA response rate <p>Safety</p> <ul style="list-style-type: none"> • AEs • SAEs • WDAE <p>Patient-reported outcomes/ QoL</p>

Table 6.1. Selection Criteria				
Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
	<ul style="list-style-type: none"> Geographical region (e.g., North America, Europe, Asia-Pacific) 			
ADT = androgen deprivation therapy; AE = adverse events; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; mg = milligram; OS = overall survival; nmCRPC = non-metastatic castrate resistant prostate cancer; PO = oral; PSA = prostate specific antigen; QoL =health-related quality of life; RCT =randomized controlled trial; SAE =serious adverse events; WDAE =withdrawal due to adverse events				

* Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)

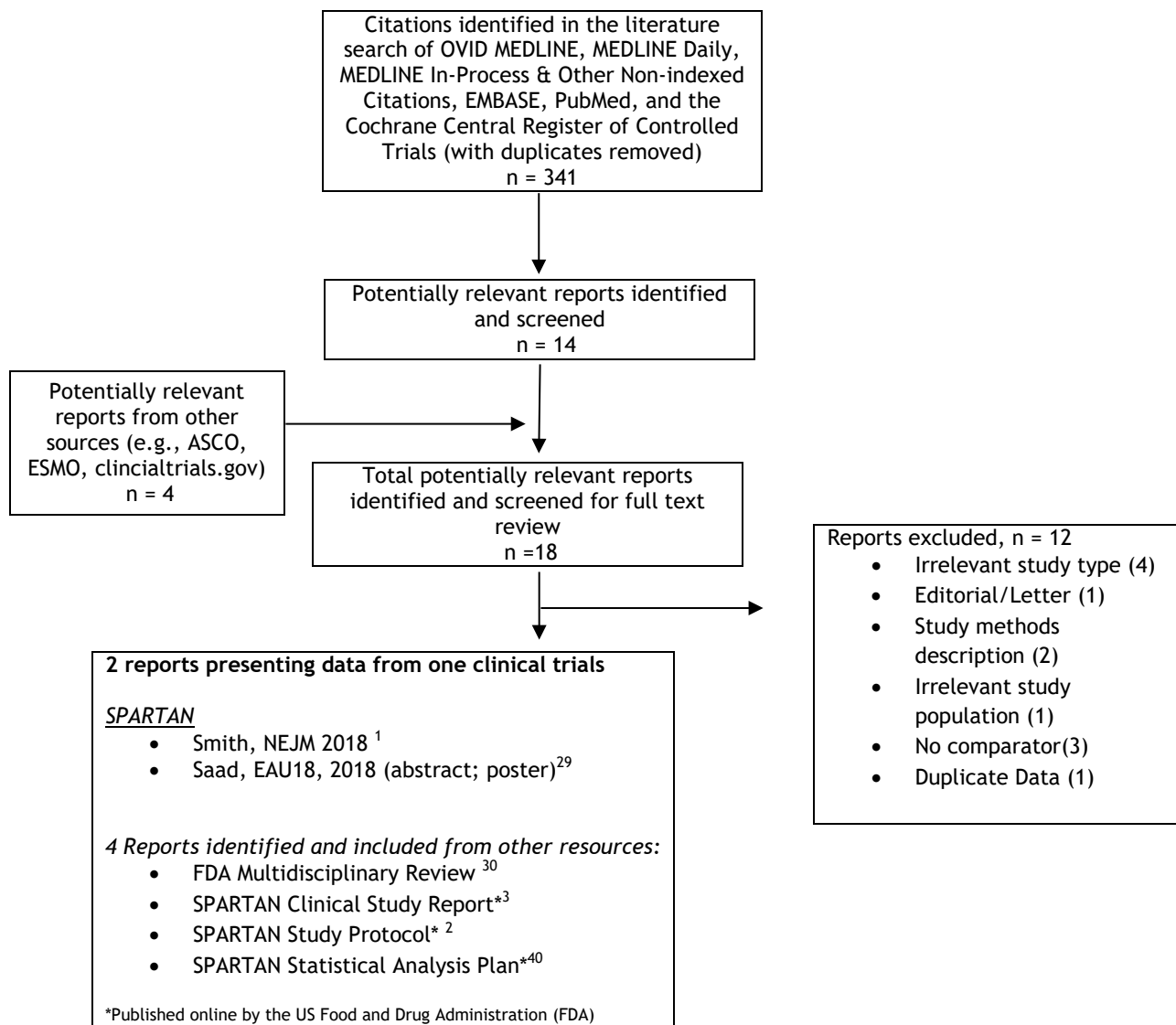
6.3 Results

6.3.1 Literature Search Results

Of the 18 potentially relevant reports identified, six reports reporting data from one clinical trial were included in the pCODR systematic review,^{1,3,29,30} and 12 studies were excluded. Studies were excluded because they had an irrelevant study design,³¹⁻³⁴ described the study design only,^{35,36} included irrelevant study population,³⁷ reported duplicate data from an already included citation,³⁸ or were published in the form of letter or editorial.³⁹ Figure 6.1 illustrates the PRISMA flow Diagram for the study selection process.

Figure 1. Sample QUOROM Flow Diagram for Inclusion and Exclusion of studies

Figure 6.1: PRISMA Flow Diagram for Inclusion and Exclusion of studies



Note: Additional data related to the SPARTAN trial were also obtained through requests to the Submitter by pCODR⁴¹

6.3.2 Summary of Included Studies

6.3.2.1 Detailed Trial Characteristics

One randomized trial met the selection criteria of this review. SPARTAN (n =1207) was a multinational, multicentre, phase 3 randomized (2:1 ratio), double-blind trial comparing apalutamide with placebo in patients with nmCRPC. Relevant information on trial characteristics is summarized below.

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
<p>SPARTAN^{1-3,29,40} (ARN-509-003) NCT01946204</p> <p>Characteristics: multinational, multicentre, phase 3 randomized (2:1 ratio), double-blind, placebo- controlled trial</p> <p>N randomized: 806 (apalutamide arm) 401 (placebo arm)</p> <p>Number treated: N= 803 (apalutamide arm) N= 398 (placebo arm)</p> <p>Number of centres and number of countries: 332 centers from 26 countries</p> <p>Patient Enrolment Dates: 14 October 2013 to 15 December 2016</p> <p>Data cut-off (primary analysis): 19 May 2017</p> <p>Estimated study completion date: August 29 2019</p> <p>Funding: Janssen Research and Development</p>	<p><u>Key Inclusion Criteria:</u></p> <ul style="list-style-type: none"> • ≥18 years of age • histologically or cytologically confirmed castration-resistant adenocarcinoma of the prostate (nmCRPC) at high-risk for metastases (PSA doubling time ≤10 months) • absence of symptomatic loco-regional lymph nodes (N0) or lymph nodes < 2 cm in the short axis (N1) located below the iliac bifurcation • ECOG performance score 0 or 1 <p><u>Key Exclusion Criteria:</u></p> <ul style="list-style-type: none"> • presence of distant metastases including CNS and vertebral or meningeal involvement or a history of distant metastases 	<p>Intervention arm : Apalutamide (240 mg per day; orally) during continuous ADT</p> <p>Control arm: Placebo (tablets matched in size, color, and shape to apalutamide tablets; orally) during continuous ADT</p> <p>Duration of treatment (both arms): Continuous daily dosing (28-day cycles) until disease progression, incidence of AEs, or withdrawal of consent</p>	<p><u>Primary:</u></p> <ul style="list-style-type: none"> • MFS (by BICR) <p><u>Secondary:</u></p> <ul style="list-style-type: none"> • TTM (by BICR) • PFS (by BICR) • Time to symptomatic progression • OS • Time to initiation of cytotoxic chemotherapy <p><u>Exploratory:</u></p> <ul style="list-style-type: none"> • Health-related quality of life and prostate cancer-specific symptoms • AEs • PSA Response • Time to PSA progression • PFS2 • Medical resource utilization
<p>ADT = androgen deprivation therapy; AE = adverse event; BICR = blinded independent central review; ECOG = Eastern Cooperative Oncology Group; MFS = metastasis-free survival; nmCRPC = non-metastatic castration resistant prostate cancer; OS = Overall survival; PFS = progression-free survival; PFS2 = second progression-free survival; PSA = prostate-specific antigen; TTM = time to metastasis</p>			

Table 6.3: Select quality characteristics of included studies of apalutamide in patients with non-metastatic castration resistant prostate cancer

Study	Treatment vs. Comparator	Primary outcome	Required sample size	Sample size	Randomization method	Allocation concealment	Blinding	ITT Analysis	Final analysis	Early termination	Ethics Approval
SPARTAN	Apalutamide vs. placebo	MFS	1200 (800 in apalutamide and 400 in placebo arms)	1207 (806 in apalutamide and 401 in placebo arms)	Computer-generated (IVRS)	Yes	Yes	Yes	Yes	No	Yes
IVRS = Interactive Voice Response System; MFS = metastasis-free survival											

a) Trials

SPARTAN

The SPARTAN trial is multinational, multicentre, randomized, double-blind, placebo-controlled phase 3 trial comparing apalutamide with placebo, when administered with concurrent androgen deprivation therapy (ADT; i.e., either bilateral orchiectomy or treatment with gonadotropin-releasing hormone (GnRH) analog agonist or antagonist). The trial was conducted in 332 centres across 26 countries in North America (including Canada: 27 centers), Europe and Asia-pacific region.^{1,3}

To be eligible for enrollment in the study patients had to be 18 years of age or older, to have a histologically or cytologically confirmed adenocarcinoma of the prostate that was castration-resistant, defined as three prostate-specific antigen (PSA) rises at least one week apart with the last PSA more than 2 ng/mL; and to be in high risk for development of metastases, defined as a prostate-specific antigen doubling time (PSADT) less than or equal to 10 months, during continuous ADT. Other eligibility criteria included: surgically or medically castrated with testosterone levels of less than 50 ng/dL, absence of symptomatic local or regional nodal disease (classified as N0 on the tumor-node-metastasis staging system) or malignant pelvic lymph nodes that measures less than 2 cm in the short axis (classified as N1), no prior treatment with next generation anti-androgens, stable doses of bone loss prevention treatment with bone-sparing agents for at least 4 weeks prior to randomization, Eastern Cooperative Oncology Group (ECOG) Performance Status 0 or 1, and adequate organ function according to the protocol-defined criteria. At least 4 weeks must have elapsed from major surgery, radiation therapy, or the use of 5- α reductase inhibitors, estrogens, and any other anti-cancer therapy prior to randomization, including chemotherapy given in the adjuvant/neoadjuvant setting.^{1,2,4}

Patients were randomized in a 2:1 ratio to receive either apalutamide (240 mg once daily) or placebo using the Interactive Voice Response System (IVRS). The randomization was stratified by the following factors:

- PSADT (>6 months vs. \leq 6 months)
- Use of bone sparing agents (yes vs. no)
- Presence of loco-regional disease (N0 vs N1).^{1,4}

The study design is illustrated in Figure 6.2. As shown, the study consisted of three phases:³⁰

- a Screening Phase of up to 35 days before randomization to establish eligibility and document baseline measurements;
- a Double-blind Treatment Phase after randomization during which apalutamide (or matching placebo) was administered orally on a continuous daily dosing (28-day treatment

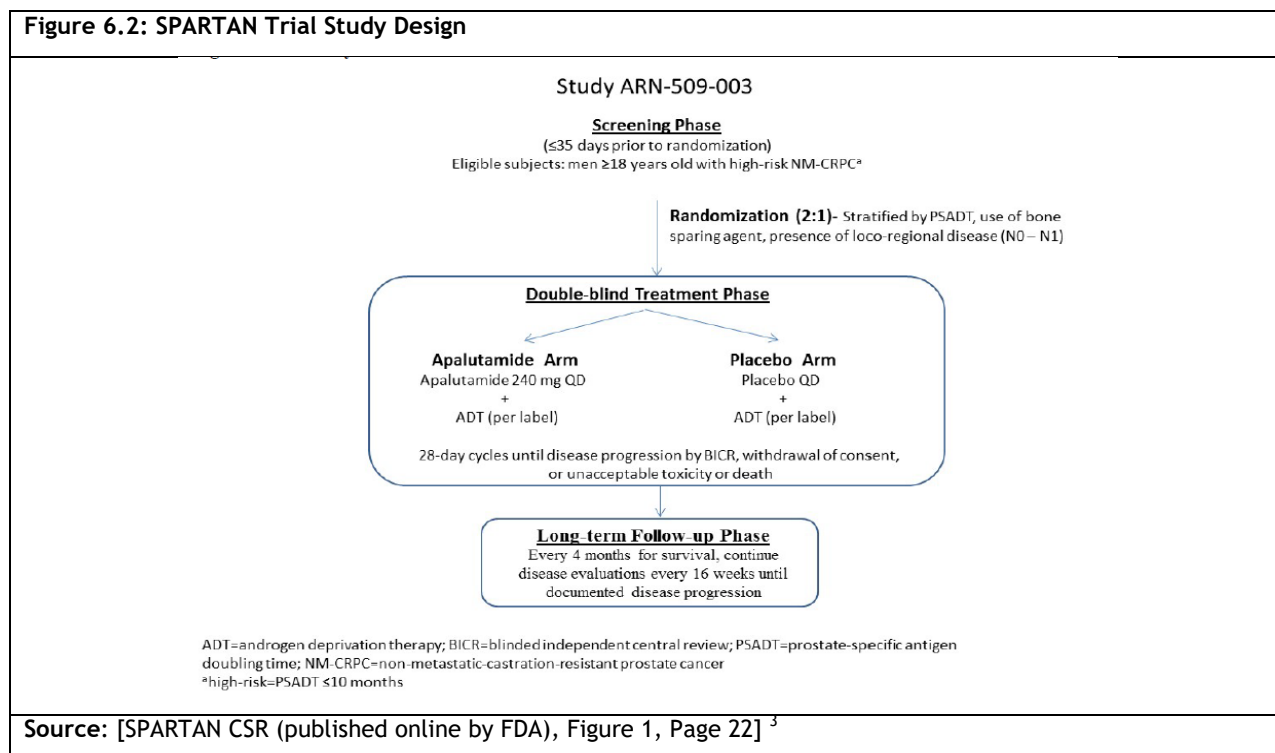
cycles). Placebo tablet was matched in size, color, and shape to apalutamide tablets in order to maintain blindness throughout the study.

- a Long-term Follow-up Phase to monitor progression-free and overall survival status, subsequent prostate cancer therapy, patient-reported outcomes, and medical resource utilization. Patients were to remain on study treatment until documented radiographic progression, withdrawal of consent, or the development of unacceptable toxicity.

Disease assessment including computerized tomography (CT), magnetic resonance imaging (MRI), and technetium-99m bone scans were performed by blinded independent central review [BICR] every 16 weeks and at additional time points, if distant metastases were suspected. Radiographic assessments were planned to be performed as scheduled according to the calendar, regardless of treatment delays due to toxicity. PSA levels were measured at a central laboratory, in order to maintain patients, trial staff, and sponsor representatives blind to the treatment assignments and patient's PSA values.^{1,2}

Patients who discontinued treatment (prior or after radiographic disease progression) also entered the Long-term Follow-up Phase. Patients who discontinued treatment due to documented radiographic progression were followed up every 4 months until death, loss of follow-up, or withdrawal of consent, whichever comes first. Patients who discontinued treatment prior to documented radiographic progression continued to have scheduled disease assessment visits every 16 weeks until documented radiographic progression; and then, were followed up every 4 months until death, loss of follow up or withdrawal of consent, whichever comes first (protocol amendment #2).²

Figure 6.2: SPARTAN Trial Study Design



The primary outcome of the study was metastasis-free survival (MFS), defined as the time from randomization to the first detection of distant metastasis on imaging (as assessed by BICR) or death from any cause, whichever occurred earlier, + 1 day. Secondary outcomes included: time to metastasis (as assessed by BICR), progression-free survival (PFS; as assessed by BICR), time to symptomatic progression, overall survival (OS), and time to the initiation of cytotoxic chemotherapy. Exploratory end points included time to PSA progression, PSA response rate,

patient-reported outcomes (assessed with the Functional Assessment of Cancer Therapy-Prostate (FACT-P) and the three-level version of the European Quality of Life-5 Dimensions (EQ-5D-3L) questionnaires), second-progression-free survival, and adverse events (AEs).^{1,2}

The trial was designed to have 90% power to detect a hazard ratio (HR) of 0.70 for MFS at a two-sided significance level (α) of 0.05. Based on the results of a phase 3 study of denosumab versus placebo in high risk NMCRPC patients,⁴² the median MFS was assumed to be 25 months in the placebo arm; and approximately 1200 patients (800 in the apalutamide arm and 400 in the placebo arm) were planned to be randomized in order to observe a 11 month increase in the median MFS (i.e., 36 months in the apalutamide arm versus 25 months in the placebo arm). An estimated number of 372 MFS events were required for the primary analysis.^{2,30} The study was also powered at 85% to detect a HR of 0.75 at a two-sided α of 0.05 for OS, based on the assumed median OS of 49 months in the placebo arm, and an expected increase of approximately 16 months in the median OS in the treatment arm (i.e., 65 months in the apalutamide arm versus 49 months in the placebo arm). For the final analysis of time to symptomatic progression, the trial was powered at 80% to detect a HR of 0.75 at a two-sided α of 0.05.³⁰

The primary analyses of efficacy outcomes included intent-to-treat (ITT) population (i.e., all randomized patients, with study drug assignments designated according to initial randomization), while the primary analysis of safety outcomes included Safety Analysis population (i.e., patients who received at least one dose of study drug, with treatment assignment designated according to actual study treatment received). A single, final, analysis was planned for the primary end point of metastasis-free survival.¹ The objective of the primary analysis was to compare MFS between the two treatment arms using a two-sided log-rank test, stratified according to the pre-specified factors at $\alpha=0.05$ significance level. A hierarchical, adaptive, group sequential procedure was used for the secondary outcomes in the following order, each at $\alpha=0.05$:

- time to metastasis
- PFS
- Time to symptomatic progression
- OS
- Time to initiation of cytotoxic chemotherapy^{2,30}

No interim analyses were planned for the secondary outcomes of time to metastasis and PFS, time to metastasis and PFS. One interim analysis was planned for time to symptomatic progression, and up to 2 interim analyses were planned for OS and time to cytotoxic chemotherapy.³⁰ The final analysis of time to metastasis and PFS, interim analysis of time to symptomatic progression, and the first interim analysis of OS and time to initiation of cytotoxic chemotherapy were performed at the same time as the primary analysis of MFS (planned after approximately 372 events). The Kaplan-Meier method was used to summarize time-to-event outcomes, and to estimate median event times. Cox proportional-hazards models were used to estimate the hazard ratios and 95% confidence intervals.^{2,3}

Other exploratory efficacy outcomes included time to PSA progression, PSA response rate, and second-progression-free survival (PFS2).²

The analysis of the patient-reported outcomes used data from a subset of the Safety Analysis population that had completed at least the baseline assessment (Cycle 1 Day 1) of either FACT-P or EQ-5D questionnaires.² A 10-point change in the FACT-P total score was considered clinically meaningful and any patient experiencing a 10-point decline in FACT-P total scores from baseline was considered to be experienced a clinically meaningful deterioration in functional status. The decrement in the FACT-P total score between treatment arms was compared using a Mantel-Haenszel test, stratified by PSADT (>6 months vs. ≤6 months), the use of a bone-sparing agent (Yes vs. No), and the presence of loco-regional disease (N0 vs. N1) at a two-sided significance level of

0.05. There was no adjustment for multiplicity. The EQ-5D results were summarized descriptively.³

A single, final analysis was planned for the primary end point of MFS and for the secondary end points of time to metastasis and PFS. The first interim analyses of OS and time to the initiation of cytotoxic chemotherapy were conducted at the time of the final analysis of MFS. Final analyses for OS and time to the initiation of cytotoxic chemotherapy are planned to be performed after 427 events have been observed for each outcome.¹

There were 8 amendments to the SPARTAN protocol. A summary of the protocol amendments are summarized in Table 6.4, and the number and proportion of patients randomized in each study group at the time of each protocol amendment are shown in Table 6.5.

Table 6.4: SPARTAN protocol amendments	
Protocol version (date)	Amendment Description
Original Protocol (5 November 2012)	
Amendment INT-1 (11 January 2013)	Removed requirement for refrigerated conditions of shipping and storage of ARN-509/placebo softgel capsules.
Amendment INT-2 (8 May 2013)	Removed ARN-509/placebo storage conditions from the protocol and presented that storage instructions are found on the packaging label Modified the description of the frequency of tumor assessments with respect to randomization date rather than first dose of study drug. Clarified that subjects should remain on study until they have disease progression confirmed by BICR. If the subject discontinues treatment before confirmed disease progression, the schedule of tumor assessment (every 16 weeks from randomization) should continue until disease progression. Modified and clarified eligibility criteria
Amendment INT-3 (11 March 2014)	Added of four secondary endpoints (time to symptomatic progression, time to initiation of cytotoxic chemotherapy, progression-free survival, and time to metastasis), and modified the statistical analysis plan for the secondary endpoints. Added exploratory biomarkers. Added of the provision of abiraterone acetate plus prednisolone as a subsequent therapy for eligible subjects (except in Japan). Removed urinalysis testing from procedures Modified pharmacokinetics and patient-reported outcome analyses.
Amendment INT-4 (16 June 2014)	Modified inclusion criteria #1 and 2 in order to clarify the definitions of PSA doubling time and castration-resistance (Amendment INT-4 was not implemented, the changes described for this amendment were incorporated in Amendment INT-5).
Amendment INT-5 (1 July 2014)	Modified the eligibility criteria to clarify the definitions of PSA doubling time and castration-resistant. Added a 24-month collection time period during which PSA values used to calculate the PSA doubling can be obtained Added an optional pre-screening period.
Amendment INT-6 (18 May 2015)	Changed formulation from softgel capsules to tablet.
Amendment 7 (1 June 2016)	Reduced clinic visit frequency from Day 1 of Cycles N (± 2 Days) to: - Every cycle up to Cycle 6 - Starting at Cycle 7 every 2 cycles (e.g., C9, C11) - Starting at Cycle 13 every 4 cycles (e.g., C17, C21). Aligned collection timing of pharmacokinetics and quality of life data with the revised visit schedule. Clarified that collection of medical resource utilization (MRU) was to continue during the Long-term Follow-up Phase.
Amendment 8 (15 March 2017)	Revised the multiple testing procedure and enacted hierarchical testing for the secondary endpoints, including a provision for re-estimating the time points for next analysis of symptomatic progression and other secondary endpoints. Added details for placebo subjects to receive apalutamide, in the event of a positive study result and unblinding. Clarified criteria for disease progression for administration of abiraterone acetate, if the study is unblinded.
Source:[FDA Multi-Disciplinary Review; SPARTAN Study Protocol] ^{2,30}	

Table 6.5: Patient randomization per protocol amendment in the SPARTAN trial

Protocol Amendment	Amendment Date	Total Patients Randomized in the Apalutamide Arm Prior to Amendment (N=806)	Total Patients Randomized in the Placebo Arm Prior to Amendment (N=401)
1	11 January 2013	0 (0%)	0 (0%)
2	08 May 2013	0 (0%)	0 (0%)
3	11 March 2014	14 (1.7%)	10 (2.5%)
4/5	01 July 2014	54 (6.7%)	31 (7.7%)
6	18 May 2015	353 (44%)	178 (44%)
7	01 June 2016	767 (95%)	381 (95%)
8	15 March 2017	806 (100%)	401 (100%)

Source: adsl.xpt, CSR for ARN-509-003 (Module 5.3.5.1)

Source: [FDA Multi-Disciplinary Review; Table 10]³⁰

b) Populations

In the SPARTAN trial, a total of 1207 patients were enrolled, and randomized to receive either apalutamide (n=806) or placebo (n=401).¹ Study participants were recruited in 26 countries in Europe, the Asia-Pacific region, and North America, including 82 patients from Canada (8% [61/806] of the patients enrolled in the apalutamide arm and 5% [21/401] of those enrolled in the placebo arm).³⁰ Twenty-eight percent of the patients, for both study arms, were enrolled in the United States (US), and approximately 50% of the study participants were from Europe (49% in the apalutamide arm and 51% in the placebo arm).¹

Demographic and disease characteristics of the ITT population are summarized in Table 6.6. Overall, the baseline characteristics were well balanced between the study arms. The median age in the ITT population was 74 years (range 48-94 years in the apalutamide arm and 52-97 in the placebo arm). The median PSA doubling time at baseline was less than 5 months in each group. The median PSA doubling time at baseline was 4.4 months for the apalutamide arm and 4.5 months for the placebo arm. The median time from initial prostate cancer diagnosis to randomization was 7.95 years in the apalutamide arm and 7.85 years in the placebo arm. About 10% of patients in each arm had a history of treatment with a bone sparing agent, and around 16% of patients in each arm presented with lymph nodes (N1).¹

The types and frequencies of prior prostate cancer treatments are summarized in Table 6.7. Based on the study reports, all 401 patients in the placebo arm and 803 of 806 patients in the apalutamide arm had received treatment for prostate disease at the baseline. No previous prostate cancer treatments were reported for 3/806 patients in the apalutamide arm. Following pCODR's request for clarification, the Manufacturer confirmed that all three patients were on GnRH analogues.⁴³ As the table shows, the proportions of patients with a history of any given therapy were well balanced between the study arms. Overall, 76.6% of patients had prior surgery or radiation therapy; 99.5% had received prior hormonal therapy, and 2% had a history of chemotherapy.³⁰

Table 6.6: Baseline characteristics of study in the SPARTAN trial (ITT population)

Characteristic	Apalutamide (N=806)	Placebo (N=401)
Age — yr		
Median	74	74
Range	48–94	52–97
Median time from initial diagnosis to randomization — yr	7.95	7.85
Prostate-specific antigen doubling time		
Median — mo	4.40	4.50
≤6 Mo — no. (%)	576 (71.5)	284 (70.8)
>6 Mo — no. (%)	230 (28.5)	117 (29.2)
Use of bone-sparing agent — no. (%)		
Yes	82 (10.2)	39 (9.7)
No	724 (89.8)	362 (90.3)
Classification of local or regional nodal disease — no. (%)		
N0	673 (83.5)	336 (83.8)
N1	133 (16.5)	65 (16.2)
Previous prostate-cancer treatment — no. (%)		
Prostatectomy or radiation therapy	617 (76.6)	307 (76.6)
Gonadotropin-releasing hormone analogue agonist	780 (96.8)	387 (96.5)
First-generation antiandrogen agent†	592 (73.4)	290 (72.3)

* There were no significant differences between groups in the demographic and disease characteristics at baseline.

† First-generation antiandrogen agents are flutamide, bicalutamide, and nilutamide.

Source: [Smith NEJM, 2018, Table 1]¹

From New England Journal of Medicine, Smith MR, Saad F, Chowdhury S, et al. Apalutamide treatment and metastasis-free survival in prostate cancer, vol. 378 iss. 15, pages:1408-1418. Copyright © 2018 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society

Table 6.7: Overall Summary of Prior Prostate Cancer Therapy; Intent-to-treat Population

	Placebo	Apalutamide	Total
ITT population	401	806	1207
Previous prostate cancer therapy			
N	401	803	1204
Surgery or radiotherapy	307 (76.6%)	617 (76.6%)	924 (76.6%)
Surgery only	69 (17.2%)	159 (19.7%)	228 (18.9%)
Radiotherapy only	85 (21.2%)	157 (19.5%)	242 (20.0%)
Both surgery and radiotherapy	153 (38.2%)	301 (37.3%)	454 (37.6%)
Hormonal therapy	400 (99.8%)	801 (99.4%)	1201 (99.5%)
GnRHa	387 (96.5%)	780 (96.8%)	1167 (96.7%)
First generation antiandrogen	290 (72.3%)	592 (73.4%)	882 (73.1%)
Orchiectomy	24 (6.0%)	47 (5.8%)	71 (5.9%)
Other	9 (2.2%)	17 (2.1%)	26 (2.2%)
Chemotherapy	7 (1.7%)	17 (2.1%)	24 (2.0%)
Other	32 (8.0%)	64 (7.9%)	96 (8.0%)

GnRHa = gonadotropin releasing hormone analog
Chemotherapy: either adjuvant or neoadjuvant

Source: [SPARTAN CSR published online by FDA, Table 8 page 57]³⁰

c) Interventions

Treatment Dosing Schedule

Patients in the apalutamide arm received apalutamide at 240 mg, orally, once daily (4 x 60-mg tablets) on a continuous dosing regimen. Patients in the placebo arm received matched placebo tablets (with no active ingredient) orally daily.^{1,2} Patients were to remain on study treatment until documented radiographic progression (development of distant metastases as assessed by BICR), withdrawal of consent, or the development of unacceptable toxicity.^{1,3} Eighty-eight percent of patients in the apalutamide arm and 93% of those in the placebo arm had more than 80% compliance.³⁰

The median duration of treatment was 16.9 months in the apalutamide arm and 11.2 months in the placebo arm. Overall, 70% of patients in the apalutamide arm received at least 12 months of treatment when compared with 45% of patients in the placebo arm. The proportion of patients who received at least 24 months of treatment was 26% for the apalutamide arm and 11% for the placebo arm³

Dose delays, reductions or modifications

For patients with treatment-related seizure of any grade the study drug had to be permanently discontinued. In patients with Grade 1-2 treatment-related AEs short treatment breaks could be employed, as per the discretion of the Investigator, until the severity of the AEs decreased to Grade 1 or returned to baseline. In patients with Grade 3-4 treatment-related AEs (other than seizure), study drug was to be held until the severity of the toxicity decreased to Grade 1 or returned to baseline. If the AEs recurred, dose could be reduced from 240 mg to 180 mg (3 x 60-mg tablets) and then to 120 mg (2 x 60-mg tablets) once daily, with the reduced number of total capsules (in the placebo arm, the number of tablets would be reduced from four to three and then to two tablets per day). Dose re-escalation was not permitted, unless discussed with the Sponsor. Participation of patients with AEs that could not be adequately managed with dose modifications, and those requiring dose interruptions longer than 28 days, could be discontinued before completion of the study, if the protocol-specified discontinuation criteria were met.²

Concomitant and subsequent interventions

Continuous treatment with a gonadotropin-releasing hormone (GnRH) analogue or surgical castration (bilateral orchiectomy) was mandatory to maintain castrate concentrations of testosterone (<50 ng/dL). Salvage radiation for loco-regional pelvic disease and surgical procedures (e.g., transurethral resection of the prostate, urethral and ureteral stent placement) to treat localized progression or symptoms were allowed.² As per the study exclusion criteria, the use of drugs known to decrease the seizure threshold and/or cause seizure were prohibited while receiving study treatment. The concurrent use of systemic corticosteroids was not recommended; however, short term use (\leq 4 weeks) was allowed if clinically indicated. In this case, corticosteroids had to be tapered off as soon as possible.²

Overall, 90.6% of the study participants (89.7% in the apalutamide arm, 92.5% in the placebo arm) received GnRH analogues. Common concomitant medications, reported for 50% or greater proportion of study participants included analgesics (61.1% in the apalutamide arm and 56.5% in the placebo arm), agents acting on the renin-angiotensin system (55.0% in the apalutamide arm and 49.7% in the placebo arm), and lipid modifying agents (50.1% in the apalutamide arm and 50.8% in the placebo arm).³

The trial permitted patients with disease progression to remain on treatment in the following conditions:³⁰

- If localized disease progression was identified by the investigator.
- If BICR imaging review identified localized-progression of disease (e.g., new or enlarging pelvic lymph nodes) without any evidence of metastatic disease.
- If metastatic disease was identified by the investigator but not confirmed by the BICR imaging reviews.
- If bone metastases were suspected by the BICR but there were no confirmatory imaging evidence (i.e., CT, MRI, or X-rays).

A total of 31 patients in the apalutamide arm who had experienced an MFS event were still on treatment at the time of the clinical cut off.⁴³

Table 6.8: Summary of subsequent systemic therapies for prostate cancer in the SPARTAN trial (ITT population)

ITT population	Placebo 401	Apalutamide 806
Number of subjects with first subsequent systemic therapy for prostate cancer ^a	222 (55.4%)	175 (21.7%)
Hormonal	193 (86.9%)	154 (88.0%)
Abiraterone	161 (72.5%)	125 (71.4%)
Enzalutamide	28 (12.6%)	20 (11.4%)
Bicalutamide	3 (1.4%)	8 (4.6%)
Flutamide	1 (0.5%)	1 (0.6%)
Chemotherapy	19 (8.6%)	15 (8.6%)
Docetaxel	18 (8.1%)	15 (8.6%)
Cabazitaxel	1 (0.5%)	0
Other	10 (4.5%)	6 (3.4%)
Sipuleucel-T	9 (4.1%)	4 (2.3%)
Investigational Drug	0	1 (0.6%)
Radium Ra 223 Dichloride	0	1 (0.6%)
Dexamethasone	1 (0.5%)	0

^a Only for this row, percent is based on using the ITT population as denominator, all the following rows use this row as the denominator.

Note: Continuing ADT is not considered as a subsequent therapy.

[TEFPC01A2.RTF] [JNJ-56021927\ARN-509-003\DBR_IA\RE_IA\PROD\TEFPC01A2.SAS] 08SEP2017, 15:39

Source: [SPARTAN CSR published online by FDA, Table 29 page 88]³

d) Patient Disposition

A total of 2,132 patients signed the informed consent and underwent screening; of those, 1207 patients were randomized to receive either apalutamide (n=806) or placebo (n=401). Of the 925 patients who failed screening, 517 patients were ineligible due to the presence of metastatic disease at screening. All randomized patients formed the ITT population. Six of the randomized patients (3 in each group) did not receive apalutamide or placebo; 803/806 of patients assigned to apalutamide and 398/401 of those assigned to placebo received the study treatment and were included in the Safety Analysis population (Figure 6.3).¹

Patient disposition during the treatment phase is presented in Table 6.9. As of 19-May-2017 data cut-off date, after a median follow-up of 20.3 months, 61% of patients in the apalutamide arm and 30% of those in the placebo arm were still receiving the assigned treatment. A total of 314 patients in the apalutamide arm (39%) and 279 patients in the placebo arm (70%) discontinued study treatment. The most common reasons for discontinuation of treatment included: progressive disease (19% in the apalutamide arm versus 52% in the placebo arm), AEs (11% in the apalutamide arm versus 6% in the placebo arm), and withdrawal by subject (7% in the apalutamide arm versus 10% in the placebo arm).^{1,30}

Figure 6.3: SPARTAN trial flow diagram

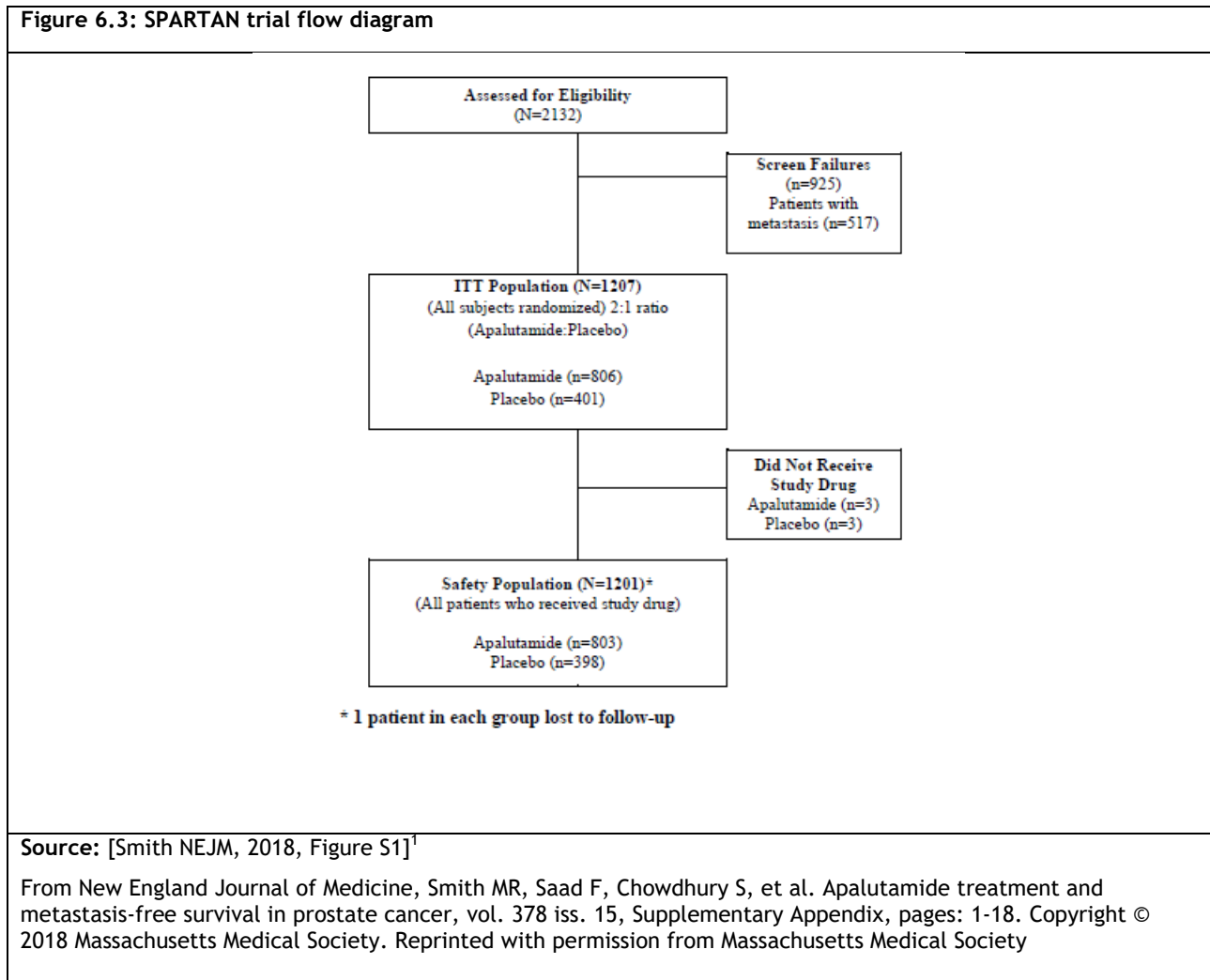


Table 6.9: Patient Disposition in the SPARTAN trial (ITT Population)

	Placebo N=401 (%)	Apalutamide N=806 (%)
Treatment status		
Ongoing	119 (30)	489 (61)
Discontinued	280 (70)	314 (39)
Reason for Treatment Discontinuation		
Progressive disease	210 (52)	155 (19)
Withdrawal by subject	40 (10)	54 (7)
Adverse event	25 (6)	86 (11)
Other	2 (0.5)	9 (1.1)
Protocol violation	2 (0.5)	3 (0.4)
Lost to follow-up	1 (0.2)	1 (0.1)
Noncompliance with study procedures	0 (0)	6 (0.7)
Study status		
Ongoing	316 (79)	687 (85)
Discontinued	85 (21)	119 (15)
Reason for Study Discontinuation		
Withdrawal by subject	37 (9)	50 (6)
Death	38 (9)	59 (7)
Other	7 (1.7)	3 (0.4)
Lost to follow-up	3 (0.7)	7 (0.9)

Source: *addisp.xpt*

Source: [FDA Multi-Disciplinary Report; Table 14, page 91]³⁰

Major protocol deviations are summarized in Table 6.10. Close to 10% of patients had at least one major protocol deviation, during the study period. The most common protocol deviation was enrollment of non-eligible patients (5.2% in the apalutamide arm and 4.0% in the placebo arm). This protocol violation was reported to mainly be related to exclusion criterion #8; i.e., concurrent therapy with any of the following that was not discontinued or substituted at least 4 weeks prior to randomization: medications known to lower the seizure threshold, herbal and non-herbal products that may decrease PSA levels, systemic corticosteroids, any other experimental treatment, and agents indicated for the prevention of skeletal-related events.³⁰

Table 6.10: Major protocol violations or deviations in the SPARTAN trial

	Apalutamide N=806 n (%)	Placebo N=401 n (%)	Total N=1207 n (%)
Patients with major protocol deviations	80 (9.9%)	37 (9.2%)	117 (9.7%)
Patients not meeting inclusion or exclusion criteria	42 (5.2%)	16 (4.0%)	58 (4.8%)
Patients receiving a disallowed concomitant treatment	21 (2.6%)	9 (2.2%)	30 (2.5%)
Patients receiving wrong treatment or incorrect dose	16 (2.0%)	9 (2.2%)	25 (2.1%)
Incorrect study treatment	3 (0.4%)	0	3 (0.2%)
Safety assessment deviation	2 (0.2%)	0	2 (0.2%)
Patients not withdrawing per protocol	0	1 (0.2%)	1 (0.1%)
Other non-compliance	2 (0.2%)	4 (1.0%)	6 (0.5%)

Source: *CSR Table 9*

Source: [FDA Multi-Disciplinary Report; Table 15, page 92]³⁰

e) *Limitations/Sources of Bias*

Overall, SPARTAN is a well-designed RCT, with the following steps taken to minimize potential biases:

- A double-blind study design to minimize bias in the assessment of all study outcomes; Investigators, patients, and the Sponsor were blinded to the results until the time of the primary analysis.
- A 2:1 randomization to increase the probability that eligible patients would be randomized to receive apalutamide, and to increase feasibility.
- A stratified randomization procedure based on known prognostic factors to minimize potential imbalances between the study groups that might lead to biased results
- Analyses of efficacy endpoints were based on radiographic tumor assessments by a blinded independent central review (BICR), provided via electronic data transfer by the third-party core imaging laboratory.
- Statistical analysis of secondary outcomes followed a hierarchical adaptive, sequential testing procedure to control for type 1 error, although exploratory endpoints (patient-reported outcomes) were not adjusted for multiplicity.

Limitations:

- During the study period, the treatment formulation was switched from a softgel capsule to a tablet (commercial formulation). Newly enrolled patients began treatment using tablets while patients who were receiving capsules made the switch to tablets at the start of a new cycle. In the safety analysis by formulation subgroups, the incidence of Gastrointestinal treatment-related AEs was highest in patients who received softgel capsules only and lowest among patients who received tablets only; the rates were similar for the placebo and active treatment arms. This difference may be attributable to excipients in the capsule formulation that are not in the tablet formulation. Also, the pill load was 8 capsules per dose compared with 4 tablets per dose. The high incidence of gastrointestinal events attributable to the capsule formulation contributed to the overall safety profile for apalutamide³
- In one site in the US and 18 sites in Canada, drug information (Canada: proforma invoices and packing list; US: packing list) sent to sites had the potential to unblind site staff and/or study monitor to the treatment arm of patients. A total of 47 patients from the sites affected had the potential to be unblinded. A sensitivity analysis was performed for MFS and safety with the 47 patients removed. The results were consistent with those of the original analyses.
- During the course of the study, it was noted that 152 subjects (13%) were inappropriately stratified at the time of randomization. Subsequent information allowed the correct stratification to be known. As a sensitivity analysis of the MFS results, a stratified analysis of MFS was performed using corrected stratification factors. The results of this analysis were consistent with those of the stratified analysis for ITT population³⁰
- All the subgroup analyses should be considered exploratory or hypothesis generating due to small sample sizes.
- Patient-reported and QoL outcomes were exploratory endpoints in the SPARTAN trial.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Efficacy Outcomes

Efficacy analyses were performed using the 1207 ITT population (806 patients in the apalutamide arm and 401 patients in the placebo arm).

Metastasis-Free Survival (MFS)

MFS was the primary outcome in the SPARTAN trial, defined as the time from randomization to the first detection of distant metastasis on imaging (as assessed by BICR) or death from any cause, whichever occurred first, +1 day. MFS data for patients without metastasis or death were censored on the date of the last tumor assessment (or, if no tumor assessment had been performed after the baseline visit, at the date of randomization + 1 day).² For regulatory purposes, additional censoring rules were applied according to the US Food and Drug Administration (FDA; referred to in the study documentations as ex-US) or the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP, referred to in the study documentations as ex-US) guidelines, as described below.²

- For patients who were lost to follow-up or whose disease progression (development of metastasis) or death occurred after two or more consecutively missing or unevaluable tumor assessments:
 - US regulatory guidance - Data would be censored on the date of the last tumor assessment that the patient was known to be metastasis-free.
 - ex-US regulatory guidance - Time of progression would be determined using the first date when there was documented evidence of progression or death (whichever occurred earlier) regardless of missed or unevaluable tumor assessments.
- For patients who received new systemic anti-cancer therapy prior to documented disease progression (development of metastasis) or death:
 - US regulatory guidance - Data would be censored on the date of the last tumor assessment prior to the start of the new systemic anti-cancer therapy.
 - ex-US regulatory guidance - Time of progression would be determined using the first date when there was documented evidence of progression or death (whichever occurred earlier) regardless of change of therapy.

Due to the small number of lost-to-follow up cases, both US and ex-US regulatory guidance techniques reportedly yielded similar results. In this pCODR review, study results will be reported based on the US censoring rules, where applicable, as they provide more conservative estimates of the treatment effect.

As of 19-May-2017 data cut-off date, after a median follow-up time of 20.3 months, distant metastasis or death had been observed in 184 patients (22.8%) in the apalutamide arm and 194 patients (48.4%) in the placebo arm. Of the patients who had metastases, 60.5% in the apalutamide arm and 54.4% in the placebo arm were reported to have bone metastases.¹ The median MFS was 40.5 months (95% confidence interval [CI] not estimable) in the apalutamide arm and 16.2 months (95% CI 14.6, 18.4) in the placebo arm. Treatment with apalutamide significantly decreased the risk of distant metastasis or death, when compared with placebo (hazard ratio [HR] = 0.28; 95% CI 0.23, 0.35; P<0.001)(Figure 6.4).^{1,3}

Subgroup analyses of MFS

Pre-specified subgroup analyses of MFS were conducted to assess the consistency of treatment effect across the following subgroups: ECOG performance status at baseline (0 vs. 1), age groups (< 65 vs. 65 to < 75 vs. ≥ 75 years), race (white, black, Asian, and others), geographic region (North America, Europe, and rest of the world), number of prior hormonal therapies (1 vs. ≥ 2), baseline PSA value (at or below median vs. above median), PSADT (> 6 months vs. ≤ 6 months), bone-sparing agent use (yes vs. no), and loco-regional disease (N0 vs. N1). The results of these subgroup analyses are presented in Figure 6.5. As shown, MFS benefit was consistent across all subgroups. No outliers were observed in the subgroup analysis; however, for the subgroup of Black men (HR = 0.63; 95% CI 0.23, 1.72) the 95% confidence interval of MFS HR crossed 1.00, which indicates a statistically non-significant treatment effect in this subgroup.^{1,3}

Figure 6.4: Metastasis-free survival, as assessed by BICR, in the SPARTAN trial

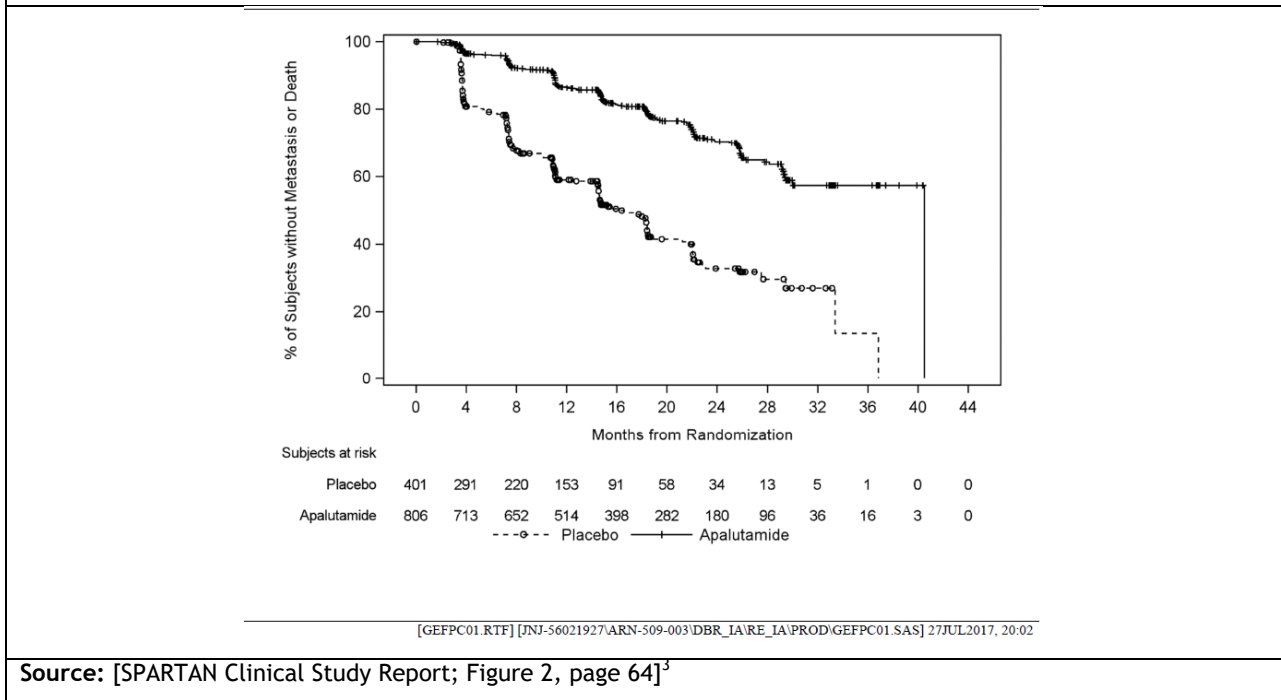
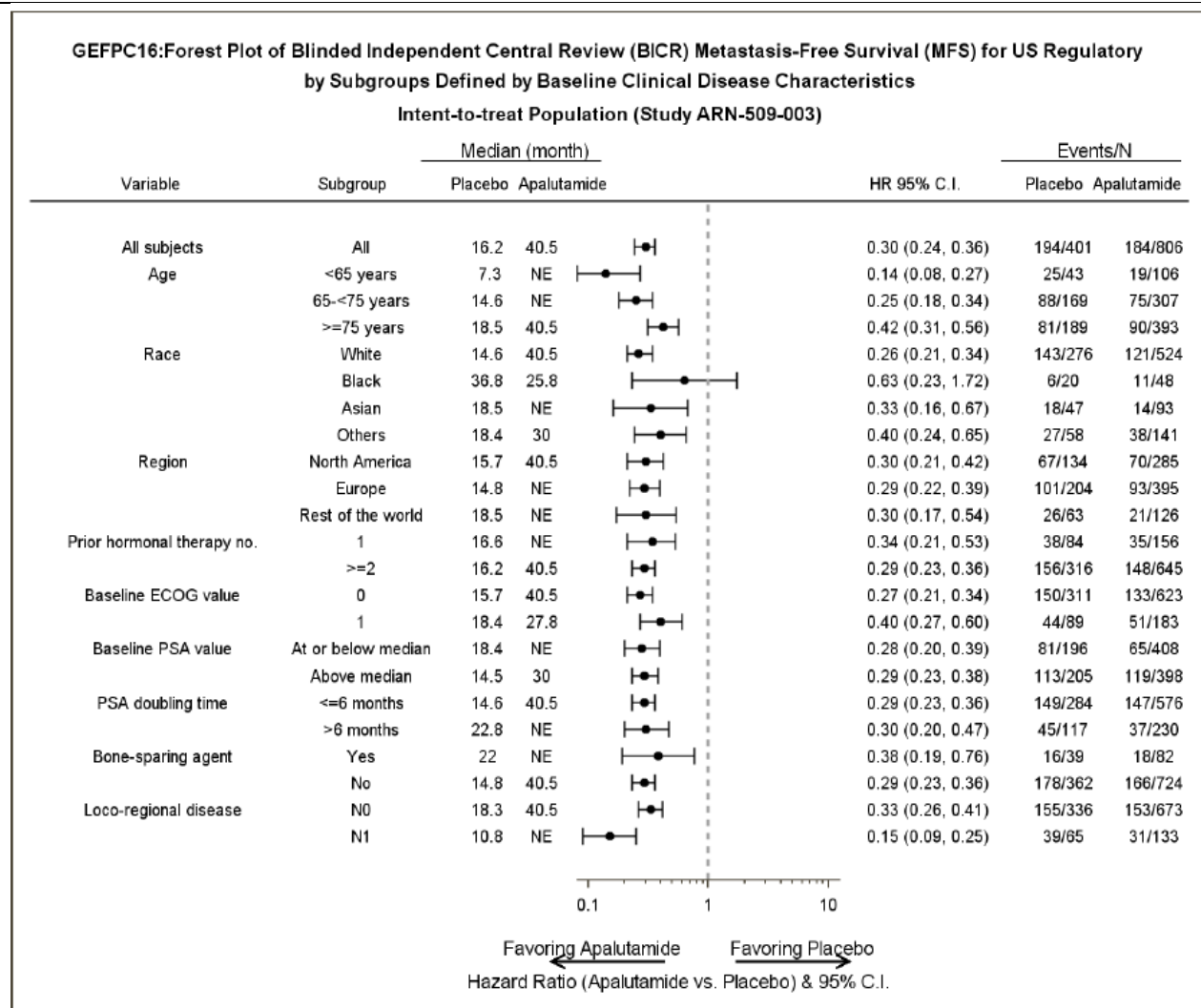


Figure 6.5: Pre-specified subgroup analyses of metastasis-free survival, as assessed by BICR, in the SPARTAN trial



Source: [SPARTAN Clinical Study Report; Figure 3, page 67]³

During the study period, the treatment formulation was switched from softgel capsule to tablet (Amendment # 6). Exploratory subgroup analyses were performed to assess the effect of treatment on MFS by formulations received. Two sets of subgroups were used: 1) Patients who received capsule only vs. patients who received both capsule and tablet vs. patients who received tablet only; and 2) patients who had a greater (1+ days) capsule treatment duration vs patients who had a greater (1+ days) tablet treatment duration.³⁰ The results of the exploratory subgroup analyses are presented in Table 6.11.

Table 6.11: Exploratory subgroup analyses of metastasis-free survival, as assessed by BICR, in the SPARTAN

trial					
	Number of Events/Total N (%)		Median (months)		HR ¹ (95% CI)
	Apalutamide + ADT	Placebo + ADT	Apalutamide + ADT	Placebo + ADT	
Formulation Set 1					
Capsule only	44/100 (44)	70/105 (67)	14.78	6.44	0.30 (0.20, 0.45)
Capsule + Tablet	98/411 (24)	78/157 (50)	40.51	22.05	0.32 (0.24, 0.43)
Tablet only	42/292 (14)	46/136 (34)	19.55	18.50	0.33 (0.22, 0.51)
Formulation Set 2					
Greater capsule treatment duration	85/169 (50)	106/155 (68)	18.43	7.75	0.39 (0.29, 0.53)
Greater tablet treatment duration	99/634 (16)	88/243 (36)	NE	22.28	0.30 (0.23, 0.41)
¹ HR is estimated from an unstratified Cox proportional hazards model Source: CSR Table 28					
Source: [FDA Multi-Disciplinary Report; Table 32, page 111] ³⁰					

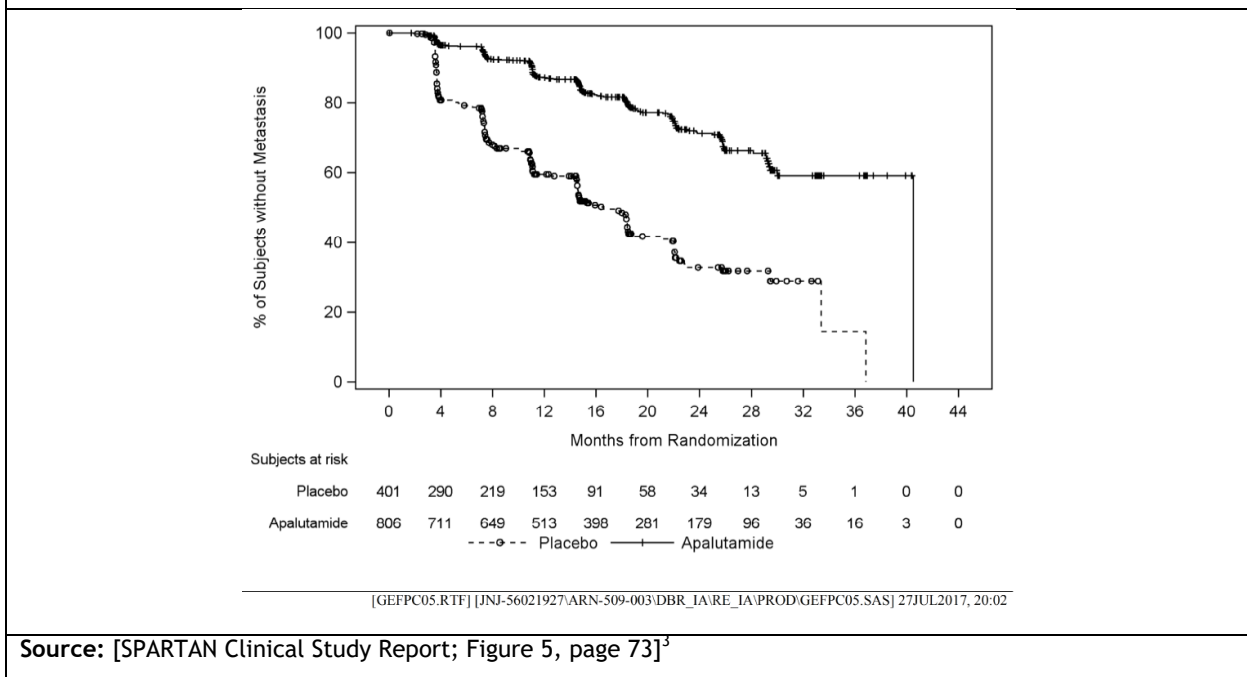
Time to Metastasis

Time to metastasis was a secondary outcome in the SPARTAN trial, defined as defined as the time from randomization to the first detection of distant metastasis involving the bone or soft tissue on imaging, as assessed by BICR.¹ Time to metastasis data for patients without metastasis were censored on the date of the last tumor assessment (or, if no tumor assessment had been performed after the baseline visit, at the date of randomization + 1 day). Additional censoring rules were applied according to the US and ex-US regulatory guidelines, as described for MFS.² According to the hierarchical testing procedure, a p-value of less than 0.05 would be considered statistically significant for time to metastasis.³⁰

As of 19-May-2017 data cut-off date, after a median follow-up time of 20.3 months, 175 patients (22%) in the apalutamide arm and 191 patients (48%) in the placebo arm had a reported metastasis event; i.e., in the stratified analysis of time to metastasis, data were censored for 78% of patients in the apalutamide arm and 52% of those in the placebo arm.³ The median estimate of BIRC-assessed time to metastasis was 40.5 months (95% CI not estimable) in the apalutamide arm and 16.6 months (95% CI 14.6, 18.5) in the placebo arm (HR = 0.27; 95% CI 0.22, 0.34; p<0.001)(Figure 6.6).^{1,30}

At 12 months, 87% of patients in the apalutamide arm and 60% of those in the placebo arm were event-free. The 24 and 36 months event-free rates were 71% and 51%, respectively, in apalutamide arm and 33% and 15%, respectively, in the placebo arm.³

Figure 6.6: Time to Metastasis, as assessed by BICR, in the SPARTAN trial



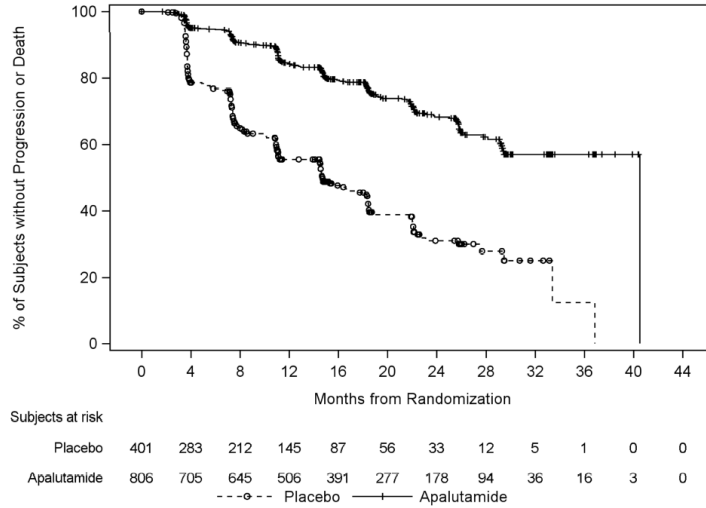
Source: [SPARTAN Clinical Study Report; Figure 5, page 73]³

Progression-Free Survival (PFS)

PFS was a secondary outcome in the SPARTAN trial, defined as the time from randomization to the first detection of local or distant metastatic disease on imaging, as assessed by BICR (based on RESICT v1.1, or death from any cause, whichever occurred first).¹ PFS data for patients without loco-regional disease were censored on the date of the last tumor assessment. Additional censoring rules were applied according to the US and ex-US regulatory guidelines, as described for MFS.²

As of 19-May-2017 data cut-off date, 200/806 patients (25%) in the apalutamide arm and 204/401 patients (51%) in the placebo arm had disease progression or died from any cause. The median PFS (Figure 6.7) was 40.5 months (95% CI not estimable) for the apalutamide arm and 14.7 months (95% CI 14.5, 18.4) for the placebo arm (HR=0.291; 95% CI: 0.238, 0.356; p<0.0001). At 12 months, 85% of patients in the apalutamide arm and 56% of those in the placebo arm were progression-free. The 24 and 36 months progression-free rates were 68% and 57%, respectively, in the apalutamide arm and 31% and 13%, respectively, in the placebo arm.³

Figure 6.7: Progression-free Survival, as assessed by BICR, in the SPARTAN trial



[GEFPC03.RTF] [JNJ-56021927\ARN-509-003\DBR_IA\RE_IA\PROD\GEFPC03.SAS] 27JUL2017, 20:02

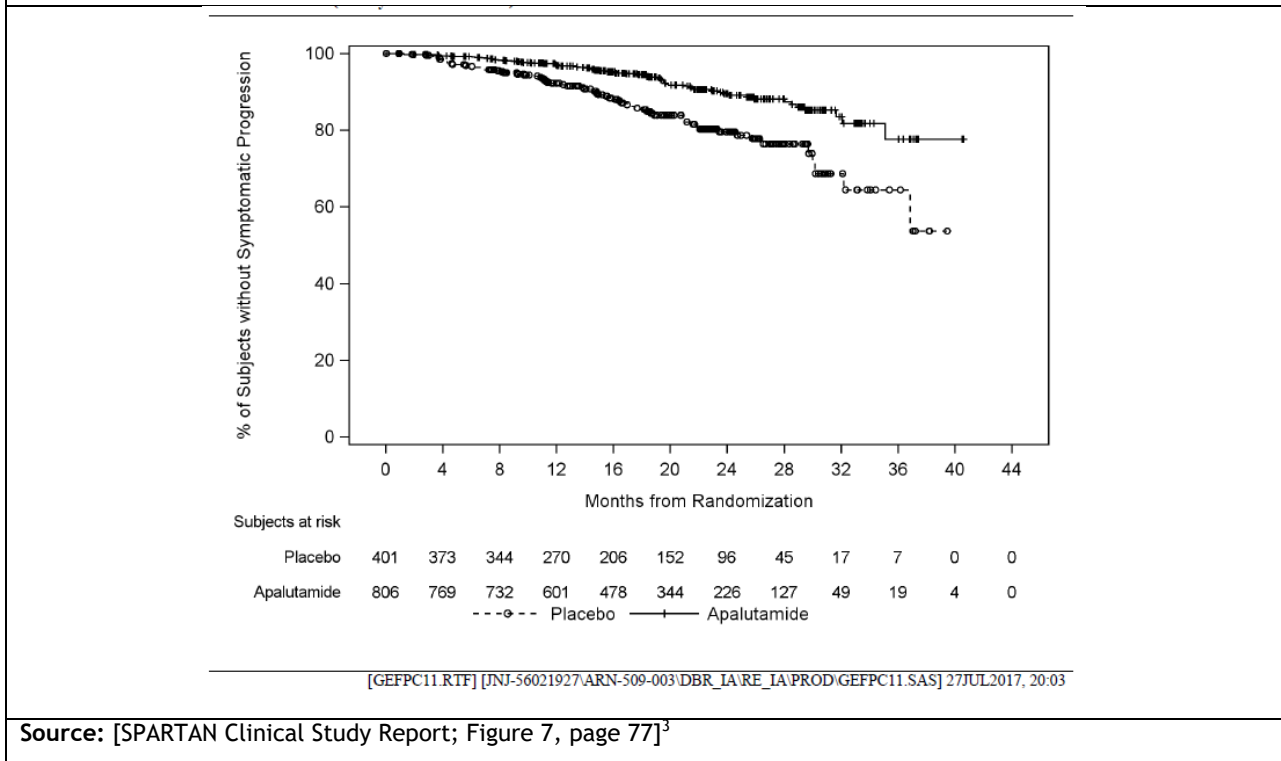
Source: [SPARTAN Clinical Study Report; Figure 6, page 75]³

Time to symptomatic progression

Time to symptomatic progression was a secondary outcome in the SPARTAN trial, defined as the time from randomization to a skeletal-related event, pain progression, or worsening of disease-related symptoms leading to the initiation of a new systemic anticancer therapy or the time to the development of clinically significant symptoms due to local or regional tumor progression leading to surgery or radiation therapy.¹ Time to symptomatic progression data for patients who did not experience any of the aforementioned events was censored on the date on which they were last known to be event-free.²

As of 19-May-2017 data cut-off date, 64/806 (7.9%) patients in the apalutamide arm and 63/401 patients (16.0%) in the placebo arm had symptomatic progression. The median time to symptomatic progression was not reached in either of the apalutamide or placebo arms (Figure 6.8). The stratified HR indicated that apalutamide resulted in a statistically significant decrease in risk of symptomatic progression, when compared with placebo (HR=0.447; 95% CI: 0.315, 0.634; p<0.0001).

Figure 6.8: Time to symptomatic progression in the SPARTAN trial



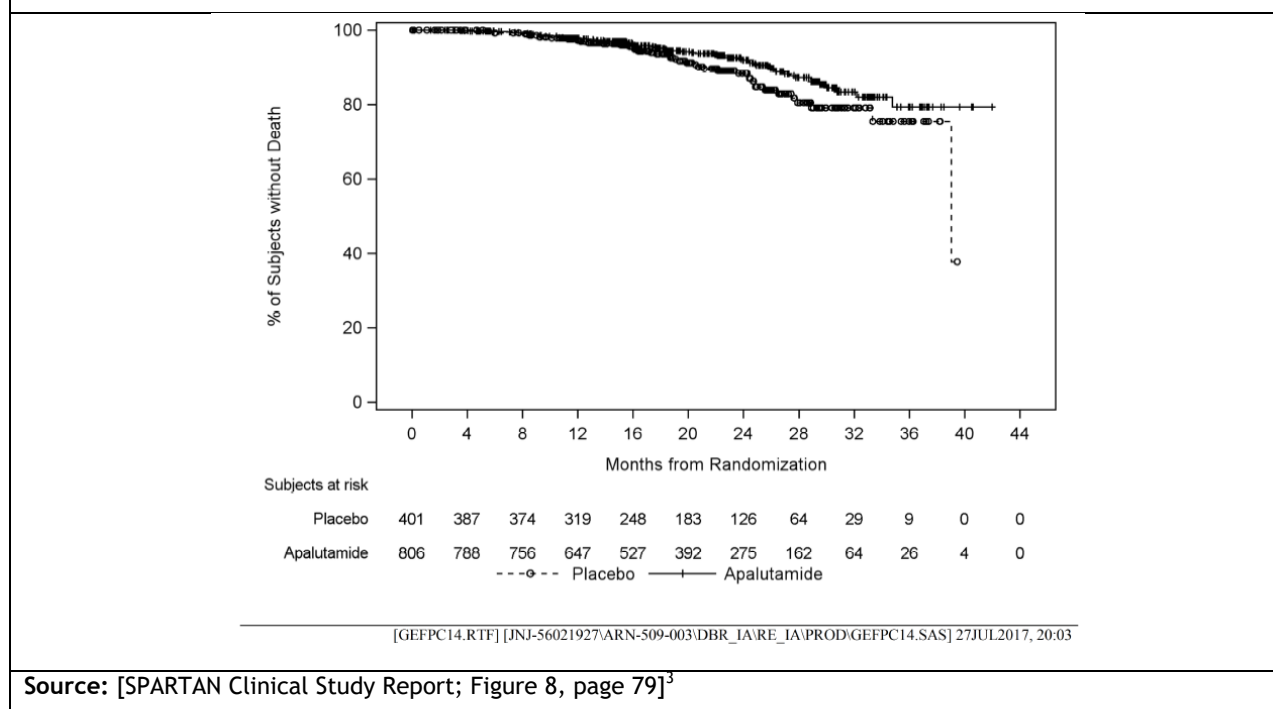
Source: [SPARTAN Clinical Study Report; Figure 7, page 77]³

Overall Survival (OS)

OS was a secondary outcome in trial, defined as the time from randomization to the date of death due to any cause +1 day. Patients who were alive at the time of the analysis were censored on the last known date that they were alive; patients with no data after the baseline were censored on the date of randomization + 1 day, and patients who were lost to follow-up or who withdrew consent for further follow-up censored on the last known date that they were alive.² OS was to be tested if the results of the analyses for MFS, time to metastasis, PFS, and time to symptomatic progression were all statistically significant. The pre-specified statistical significance level based on the O'Brien-Fleming efficacy boundary was $p=0.000012$.³

As of 19-May-2017 data cut-off date (first preplanned interim analyses of OS), 104 deaths had occurred in the ITT population (62/806 patients [7.7%] in the apalutamide arm and 42/401 patients [10.0%] in the placebo arm). The proportion of patients who were censored in this analysis was 92% for apalutamide and 90% for placebo.³ The median OS was not reached in the apalutamide arm and was 39.0 months in the placebo arm (Figure 6.9). The stratified HR indicated that OS was not statistically different between the treatment groups (HR=0.700; 95% CI: 0.472, 1.038; $p=0.0742$).³

Figure 6.9: Overall Survival, as assessed by BICR, in the SPARTAN trial



Source: [SPARTAN Clinical Study Report; Figure 8, page 79]³

Time to initiation of cytotoxic chemotherapy

Time to initiation of cytotoxic chemotherapy was a secondary outcome in the SPARTAN trial, defined as the time from randomization to documentation of a new cytotoxic chemotherapy being administered to the patient +1 day. Patients who did not start cytotoxic chemotherapy were censored on the date of last contact.² A formal statistical analysis for this outcome was to be performed if MFS, time to metastasis, PFS, time to symptomatic progression, and OS were all statistically significant.³

As of 19-May-2017 data cut-off date, the median time to the initiation of cytotoxic chemotherapy was not reached in either the apalutamide or the placebo treatment arms. Data from 94% of patients in the apalutamide arm and 89% of patients in the placebo arm were censored in this analysis.³ The stratified HR indicated a decreased risk of initiation of cytotoxic chemotherapy in the apalutamide group (HR=0.435; 95% CI: 0.286, 0.661; nominal p<0.0001). However, the HR is not considered statistically significant because, according to hierarchical testing procedures this outcome cannot be formally tested, when OS is not statistically significant.

Second-progression-free survival (PFS2)

PFS2 (PFS with the first subsequent therapy) was an exploratory outcome in the SPARTAN trial, defined as the time from randomization to investigator-assessed disease progression during first subsequent anti-cancer therapy, or death due to any cause, prior to the start of the second subsequent anti-cancer therapy, whichever occurred first.²

As of 19-May-2017 data cut-off date, 91/806 patients (11.3%) in the apalutamide arm and 78/401 patients (19.5%) in the placebo arm had disease progression the first subsequent therapy or died from any cause. The median PFS2 was not reached in the apalutamide arm and was 39.0 months (95% CI 30.2, 39.0) in the placebo arm (HR= 0.489; 95% CI: 0.361, 0.662; p<0.0001).³

Prostate Specific Antigen (PSA) response rate

PSA response rate was an exploratory outcome in the SPARTAN trial, defined as the percentage of patients who had a decline from baseline in the PSA level of at least 50%, according to Prostate Cancer Working Group 2 (PCWG2) criteria. The treatment effect in terms of PSA response was estimated using the relative risk (RR; and 2-tailed 95% CIs), and the study arms were compared using the stratified Cochran-Mantel-Haenszel test.^{2,3}

A PSA response (confirmed by a central laboratory measurement obtained ≥ 4 weeks post-baseline) was observed in 723/806 (89.7%) patients in the apalutamide arm and 9/401 (2.2%) of patients in the placebo arm (RR= 40.090; 95% CI 20.987, 76.582; $p < 0.0001$).³

Time to PSA progression

Time to PSA progression was also an exploratory outcome in the SPARTAN trial, defined as the time from randomization to PSA progression, according to PCWG2 criteria +1 day. Kaplan-Meier methods were used to estimate the median time to PSA progression for each arm and the related 95% CIs.^{3,2}

At the 19-May-2017 data cut-off date, time to PSA progression was documented for 192/806 (24%) patients in the apalutamide arm and 334/401 (83%) patients in the placebo arm (HR=0.064; 95% CI 0.052, 0.080; $p < 0.0001$). The median time to PSA progression was not reached in the apalutamide arm and was 3.7 months (95% CI 3.7, 3.8) in the placebo arm.³

Quality of Life (QoL)

QoL was an exploratory outcome in the SPARTAN trial, and was assessed in a subset of the Safety Analysis population that completed at least the baseline assessment (Cycle 1 Day 1) of either FACT-P or EQ-5D questionnaires.² Physical well-being, social/family well-being, emotional well-being, pain and prostate cancer specific symptoms were assessed using the FACT-P questionnaire, while the EQ-5D questionnaire was used to assess health status, mobility, self-care, usual activity, pain or discomfort, and anxiety and depression.²⁹ The compliance rates for completion of both FACT-P and EQ5D questionnaires were $\geq 92\%$ (range 92% to 100%) at any assessment visit during the treatment phase, and 63% or greater (range 63% to 76%) for the 'end of treatment' and follow up visits.³

The Functional Assessment Cancer Therapy-Prostate (FACT-P) questionnaire

Baseline FACT-P total scores and subscale scores were reported to be comparable between the study arms, although no formal statistical testing was conducted to test potential differences between the study groups at the baseline and during the study visits. Table 6.12 summarizes the median time to a clinically meaningful (i.e., 10 point) decline in FACT-P total score and subscale scores in the apalutamide and placebo arms. No statistically significant differences were reported in terms of the time to a clinically meaningful change in scores of the FACT-P between the apalutamide and placebo arms during the treatment and follow-up phases. No statistically significant differences were found between the treatment arms in terms of mean changes in FACT-P total score and subscale scores from baseline for almost all assessment points during the treatment phase, end of treatment visit, and follow up phases.³

The European Quality of Life-5 Dimensions (EQ-5D-3L) three level questionnaire

Baseline scores were reported to be similar between the study arms across the EQ-5D dimensions (i.e., mobility, self-care, usual activity, pain or discomfort, and anxiety and depression) and EQ VAS mean scores. For all time points, no differences between the apalutamide and placebo arms were observed in change from baseline across the EQ-5D dimensions or EQ-VAS.³

During treatment and follow-up phases FACT-P total and subscales and EQ-5D scores were maintained in the Apalutamide arm. However this was only reported descriptively and no formal statistical testing was conducted to confirm QoL was maintained.

Table 6.12: Summary of FACT-P Total and Subscale scores

	Time to Event (Months) Median (95% CI)		Hazard Ratio ^a (95% CI)
	Placebo N=401	Apalutamide N=806	
FACT-P total	8.38 (6.47, 12.91)	6.60 (5.55, 7.92)	1.062 (0.904,1.247)
PWB	7.43 (5.59, 11.10)	6.57 (5.55, 8.38)	1.023 (0.871,1.203)
SFWB	4.90 (3.84, 8.38)	7.46 (5.59, 11.07)	0.885 (0.749,1.044)
EWB	14.75 (10.61, NE)	12.98 (10.87, 18.43)	1.081 (0.904,1.292)
FWB	6.51 (4.70, 9.26)	4.63 (3.78, 5.59)	1.170 (0.998,1.373)
FACT-G	12.25 (8.38, 18.50)	9.26 (7.39, 12.94)	1.068 (0.900,1.266)
PCS	3.78 (2.86, 4.80)	3.84 (3.71, 4.70)	0.978 (0.842,1.135)
TOI	11.07 (8.31, 14.82)	7.39 (6.47, 9.26)	1.122 (0.950,1.325)
PRS	4.63 (3.71, 5.65)	5.85 (5.49, 6.90)	0.923 (0.792,1.076)
FAPSI	6.47 (4.73, 7.49)	6.51 (5.42, 7.52)	0.955 (0.818,1.116)

FACT-P= Functional Assessment Cancer Therapy-Prostate; FACT-P subscales: EWB=emotional well-being; FACT-G= Functional Assessment Cancer Therapy-General; FWB= functional well-being; PWB= physical well-being; PCS= prostate cancer; SFWB= social/family well-being; TOI= total outcome index; PRS= Pain related subscale; FAPSI= pain, fatigue, weight loss, urinary difficulties, concern about the condition becoming worse; NE= not estimable
^a Hazard ratio is from stratified proportional hazards model. Hazard ratio < 1 favors active treatment.

Source: [SPARTAN Clinical Study Report; Table 25, page 83]³

Harms Outcomes

Safety was an exploratory outcome in the SPARTAN trial. Adverse events were graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0.² All treatment-emergent AEs (TEAEs) were reported from the time informed consent was obtained until 28 days after the last dose of the study treatment.³ Safety Population consisted of 1201 patients who received at least one dose of either apalutamide or placebo (803 patients in the apalutamide arm and 398 patients in the placebo arm)^{1,3}

AEs of any cause were reported in almost all subjects in the apalutamide and placebo arms.³ Table 6.13 summarizes treatment-related AEs in the Safety Population. As shown in the table, 775/803 (97%) patients in the apalutamide arm and 371/398 (93%) patients in the placebo arm were reported with a treatment-related AEs. The most frequently reported TEAEs were fatigue (30% with apalutamide versus 21% with placebo), hypertension (25% with apalutamide versus 20% with placebo), skin rash (24% with apalutamide versus 5.5% with placebo), diarrhea (20% with apalutamide versus 15% with placebo), falls (16% with apalutamide versus 9% with placebo), fractures (12% with apalutamide versus 6.5% with placebo), and hypothyroidism (2% with apalutamide versus 8% with placebo).³

Most fractures were grade 1 or 2 AEs and did not require surgical intervention. Approximately 10% of patients were receiving bone sparing agents for osteoporosis or osteopenia at study entry. In patients who were not receiving a bone sparing agent at study entry, the incidence of fracture was reported to be 11% (82/722) in the apalutamide arm and 6% (22/359) in the placebo arm. In patients who were receiving a bone sparing agent at study entry, fractures were reported in 15% (12/81) of patients in the apalutamide arm, and 10% (4/39) of those in the placebo arm.³

Grade 3-4 treatment-related AEs were reported in 362/803 (45%) patients in the apalutamide arm and 136/398 (34%) patients in the placebo arm. Overall, 11% (85/803) of patients in the apalutamide arm and 7% (28/398) of those in the placebo arm discontinued treatment due to TEAEs. Serious AEs were reported in 25% of patients in the apalutamide arm and 23% of those in the placebo arm. Grade 3 fractures were reported in 2.7% of patients in the apalutamide arm and 0.8% of patients in the placebo arm. Serious AEs of fracture were reported in 3.4% of patients in the apalutamide arm and 0.8% of those in the placebo arm.³

TEAEs leading to death were reported for 10/803 (1.2%) patient in the apalutamide arm, and 1/398 patient (0.3%) in the placebo arm (Table 6.13).³ During the study period, a total of 47 subjects from one site in the US and 18 sites in Canada were subject to potential unblinding, due to drug information (Canada: proforma invoices and packing list; US: packing list) that had been sent to the study sites. The results of the descriptive analysis performed after removal of data for 47 patients with potential unblinding issues consistent with the TEAEs rates for the Safety Population.³

Table 6.13: Summary of treatment-related adverse events in SPARTAN trial (Safety Population)

Safety Population	Placebo 398	Apalutamide 803
Number of subjects with TEAE	371 (93.2%)	775 (96.5%)
Drug-related ^a	216 (54.3%)	565 (70.4%)
Number of subjects with Grade 3-4 TEAE	136 (34.2%)	362 (45.1%)
Drug-related ^a	17 (4.3%)	113 (14.1%)
Number of subjects with treatment-emergent SAEs ^b	92 (23.1%)	199 (24.8%)
Drug-related ^a	6 (1.5%)	31 (3.9%)
Grade 3-4	76 (19.1%)	150 (18.7%)
Number of subjects with TEAE leading to treatment discontinuation	28 (7.0%)	85 (10.6%)
Drug-related ^a	8 (2.0%)	58 (7.2%)
Number of subjects with TEAE leading to death	1 (0.3%)	10 (1.2%)
Drug-related ^a	0	1 (0.1%)
All deaths within 28 days of last dose	1 (0.3%)	10 (1.2%)
Adverse event	1 (0.3%)	7 (0.9%)
Death due to prostate cancer	0	3 (0.4%)
Other	0	0

Key: TEAE=treatment-emergent adverse event; SAE=serious adverse event.
^a Adverse events reported as related.
^b Excludes Grade 5.

Note: Percent is based on the Safety population.
Note: Treatment-emergent adverse events are those that occurred between the date of 1st dose of study drug and date of last dose of study drug +28 days. For each category, subjects are counted only once, even if they experienced multiple events in that category.

[TSFAE01.RTF] [JNJ-56021927\ARN-509-003\DBR_IA\RE_IA\PROD\TSFAE01.SAS] 27JUL2017, 20:10

Source: [SPARTAN Clinical Study Report; Table 31, page 93]³

6.4 Ongoing Trials

No ongoing trials were identified as being relevant to this review.

7 SUPPLEMENTAL QUESTIONS

There were no supplemental questions identified for this review.

8 COMPARISON WITH OTHER LITERATURE

The pCODR Clinical Guidance Panel and the pCODR Methods Team did not identify other relevant literature providing supporting information for this review.

9 ABOUT THIS DOCUMENT

This Clinical Guidance Report was prepared by the pCODR Genitourinary Clinical Guidance Panel and supported by the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding the clinical evidence available apalutamide (Erleada) for non-metastatic castration resistant prostate cancer. Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant pCODR Economic Guidance Report. Details of the pCODR review process can be found on the CADTH website (www.cadth.ca/pcodr).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the pCODR Disclosure of Information Guidelines. There was no non-disclosable information in the Clinical Guidance Report provided to pERC for their deliberations.

This Final Clinical Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Clinical Guidance Report supersedes the Initial Clinical Guidance Report. Note that no revision was made in between posting of the Initial and Final Clinical Guidance Reports.

The Genitourinary Clinical Guidance Panel is comprised of three medical oncologists. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package, which is available on the CADTH website (www.cadth.ca/pcodr). Final selection of the Clinical Guidance Panels was made by the pERC Chair in consultation with the pCODR Executive Director. The Panel and the pCODR Methods Team are editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

APPENDIX A: LITERATURE SEARCH STRATEGY AND DETAILED METHODOLOGY

1. Literature search via OVID platform

Database(s): **EBM Reviews - Cochrane Central Register of Controlled Trials** March 2018, **Embase** 1974 to 2018 April 19, **Ovid MEDLINE(R) ALL** 1946 to April 19, 2018

Search Strategy:

#	Searches	Results
	(erleada* or apalutamide* or apalutamidum* or apalutamida* or ARN 509 or ARN509 or JNJ 56021927	
1	or JNJ56021927 or JNJ 927 or JNJ927 or UNII4T36H88UA7 or 4T36H88UA7 or A52).ti,ab,ot,kf,kw,hw,rn,nm.	488
2	1 use medall	154
3	1 use cctr	20
4	2 or 3	174
5	*apalutamide/	29
6	(erleada* or apalutamide* or apalutamidum* or apalutamida* or ARN 509 or ARN509 or JNJ 56021927 or JNJ56021927 or JNJ 927 or JNJ927 or A52).ti,ab,kw,dq.	476
7	5 or 6	479
8	7 use oemez	316
9	conference abstract.pt.	3006223
10	limit 9 to yr="2013 -Current"	1813375
11	8 and 10	61
12	8 not 9	229
13	11 or 12	290
14	4 or 13	464
15	limit 14 to english language	443
16	remove duplicates from 15	316

2. Literature search via PubMed

A limited PubMed search was performed to capture records not found in MEDLINE.

Search	Add to builder	Query	Items found	Time
#3	Add	Search #1 AND #2	7	10:36:41
#2	Add	Search publisher[sb]	516581	10:36:33
#1	Add	Search Apalutamide[supplementary concept] OR erleada*[tiab] OR apalutamid*[tiab] OR ARN 509[tiab] OR ARN509[tiab] OR JNJ 56021927[tiab] OR JNJ56021927[tiab] OR JNJ927[tiab] OR JNJ 927[tiab] OR A52[tiab] OR UNII4T36H88UA7[rm] OR 4T36H88UA7[rm]	142	10:36:23

3. Cochrane Central Register of Controlled Trials (Central)
Searched via Ovid

4. Grey Literature search via:

Clinical Trial Registries:

U.S. NIH ClinicalTrials. gov
<http://www.clinicaltrials.gov/>

Canadian Partnership Against Cancer Corporation. Canadian Cancer Trials
<http://www.canadiancancertrials.ca/>

Search: Erleada/apalutamide, non-metastatic castration-resistant prostate cancer (nmCRPC)

Select international agencies including:

Food and Drug Administration (FDA):
<http://www.fda.gov/>

European Medicines Agency (EMA):
<http://www.ema.europa.eu/>

Search: Erleada/apalutamide, non-metastatic castration-resistant prostate cancer (nmCRPC)

Conference abstracts:

American Society of Clinical Oncology (ASCO)
<http://www.asco.org/>

European Society for Medical Oncology (ESMO)
<http://oncologypro.esmo.org/Meeting-Resources>

Search: Erleada/apalutamide, non-metastatic castration-resistant prostate cancer (nmCRPC) - last 5 years

Detailed Methodology of Literature Review

The literature search was performed by the pCODR Methods Team using the search strategy provided in Appendix A.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-) with in-process records & daily updates via Ovid; Embase (1974-) via Ovid; The Cochrane Central Register of Controlled Trials (March 2018) via Ovid; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Apalutamide - Erleada.

No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English-language documents, but not limited by publication year.

The search is considered up to date as of July 31, 2018.

Grey literature (literature that is not commercially published) was identified by searching the websites of regulatory agencies (Food and Drug Administration and European Medicines Agency), clinical trial registries (U.S. National Institutes of Health - clinicaltrials.gov and Canadian Partnership Against Cancer Corporation - Canadian Cancer Trials), and relevant conference abstracts. Conference abstracts were retrieved through a search of the Embase database limited to the last five years. Abstracts from the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) were searched manually for conference years not available in Embase. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the Clinical Guidance Panel. In addition, the manufacturer of the drug was contacted for additional information as required by the pCODR Review Team.

Study Selection

One member of the pCODR Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. One member of the pCODR Methods Team independently made the final selection of studies to be included in the review.

Included and excluded studies (with reasons for exclusion) are identified in section 6.3.1.

Quality Assessment

Assessment of study bias was performed by one member of the pCODR Methods Team with input provided by the Clinical Guidance Panel and other members of the pCODR Review Team. SIGN-50 Checklists were applied as a minimum standard. Additional limitations and sources of bias were identified by the pCODR Review Team.

Data Analysis

No additional data analyses were conducted as part of the pCODR review.

Writing of the Review Report

This report was written by the Methods Team, the Clinical Guidance Panel and the pCODR Secretariat:

- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.

- The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions on the net clinical benefit of the drug.
- The pCODR Secretariat wrote summaries of the input provided by patient advocacy groups, by the Provincial Advisory Group (PAG), and by Registered Clinicians.

REFERENCES

1. Smith MR, Saad F, Chowdhury S, et al. Apalutamide treatment and metastasis-free survival in prostate cancer. *N Engl J Med*. 2018;378(15):1408-1418.
2. Aragon Pharmaceuticals. Clinical study protocol: SPARTAN (selective prostate AR targeting with ARN-509). *Protocol ARN-509-003*. Rockville (MD): U.S. Food and Drug Administration: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/rev_210951_arn-509-003_PRO_Redacted.pdf. Accessed 2018 Jul 29.
3. Aragon Pharmaceuticals. Clinical study report: a multicenter, randomized, double-blind, placebo-controlled, phase III study of ARN-509 in men with non-metastatic (M0) castration-resistant prostate cancer. Selective prostate AR targeting with ARN-509 (SPARTAN). Rockville (MD): U.S. Food and Drug Administration; 2017: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/rev_210951_arn-509-003_CSR_Redacted.pdf. Accessed 2018 Jul 29.
4. Aragon Pharmaceuticals. NCT01946204: A study of apalutamide (ARN-509) in men with non-metastatic castration-resistant prostate cancer (SPARTAN). *ClinicalTrials.gov*. Bethesda (MD): U.S. National Library of Medicine; 2018: <https://clinicaltrials.gov/ct2/show/record/NCT01946204>. Accessed 2018 July 29.
5. Canadian Cancer Society. Canadian cancer statistics 2017. Special topic: pancreatic cancer. 2017; <http://www.cancer.ca/~media/cancer.ca/CW/cancer%20information/cancer%20101/Canadian%20cancer%20statistics/Canadian-Cancer-Statistics-2017-EN.pdf?la=en>. Accessed 2018 Jun 27.
6. Smith MR, Saad F, Oudard S, et al. Denosumab and bone metastasis-free survival in men with nonmetastatic castration-resistant prostate cancer: exploratory analyses by baseline prostate-specific antigen doubling time. *J Clin Oncol*. 2013;31:3800-3806.
7. Dearnaley DP, Mason MD, Parmar MK, Sanders K, Sydes MR. Adjuvant therapy with oral sodium clodronate in locally advanced and metastatic prostate cancer: long-term overall survival results from the MRC PR04 and PR05 randomised controlled trials. *Lancet Oncol*. 2009;10(9):872-876.
8. Nelson JB, Love W, Chin JL, et al. Phase 3, randomized, controlled trial of atrasentan in patients with nonmetastatic, hormone-refractory prostate cancer. *Cancer*. 2008;113(9):2478-2487.
9. Miller K, Moul JW, Gleave M, et al. Phase III, randomized, placebo-controlled study of once-daily oral zibotentan (ZD4054) in patients with non-metastatic castration-resistant prostate cancer. *Prostate Cancer Prostatic Dis*. 2013;16(2):187-192.
10. Mason MD, Sydes MR, Glaholm J, et al. Oral sodium clodronate for nonmetastatic prostate cancer – results of a randomized double-blind placebo-controlled trial: Medical Research Council PR04 (ISRCTN61384873) *J Natl Cancer Inst*. 2007;99(10):765-776.
11. Smith MR, Kabbinavar F, Saad F, et al. Natural history of rising serum prostate-specific antigen in men with castrate nonmetastatic prostate cancer. *J Clin Oncol*. 2005;23(13):2918-2925.
12. Beer TM, Armstrong AJ, Rathkopf DE, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. *N Engl J Med*. 2014;371(5):424-433.
13. Ryan CJ, Smith MR, Fizazi KS, F., Mulders PFA, Sternberg CN, Miller K. Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naïve men with metastatic castration-resistant prostate cancer (COU-AA-302): final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. *Lancet Oncol*. 2015;16:152-160.

14. Kyriakopoulos CE, Chen YH, Carducci MA, et al. Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer: Long-Term Survival Analysis of the Randomized Phase III E3805 CHAARTED Trial. *J Clin Oncol*. 2018;36(11):1080-1087.
15. Fizazi K, Tran N, Fein L, et al. Abiraterone plus Prednisone in Metastatic, Castration-Sensitive Prostate Cancer. *N Engl J Med*. 2017;377(4):352-360.
16. Saad F, Chi KN, Finelli A, et al. The 2015 CUA-CUOG Guidelines for the management of castration-resistant prostate cancer (CRPC). *Can Urol Assoc J*. 2015;9(3-4):90-96.
17. Luo J, Beer TM, Graff JN. Treatment of Nonmetastatic Castration-Resistant Prostate Cancer. *Oncology (Williston Park)*. 2016;30(4):336-344.
18. Ryan CJ, Smith MR, de Bono JS, et al. Abiraterone in metastatic prostate cancer without previous chemotherapy-naïve men with metastatic castration-resistant prostate cancer (COU-AA-302): final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. *N Engl J Med*. 2015;368(2):138-148.
19. Tannock IF, de Wit R, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med*. 2004;351(15):1502-1512.
20. Parker C, Nilsson S, Heinrich D, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. *N Engl J Med*. 2013;369(3):213-223.
21. de Bono JS, Oudard S, Ozguroglu M, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. *Lancet*. 2010;376(9747):1147-1154.
22. Fizazi K, Scher HI, Molina A, et al. Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study. *Lancet Oncol*. 2012;13(10):983-992.
23. Scher HI, Fizazi K, Saad F, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. *N Engl J Med*. 2012;367(13):1187-1197.
24. Macomson B, Lin JH, Tunceli O, et al. Time to metastasis or death in non-metastatic castrate resistant prostate cancer (nmCRPC) patients by National Comprehensive Cancer Network (NCCN) risk groups. *J Clin Oncol*. 2017;35(15_suppl):5027-5027.
25. Tombal B. Non-metastatic CRPC and asymptomatic metastatic CRPC: which treatment for which patient? *Ann Oncol*. 2012;23 Suppl 10:x251-258.
26. Fujimura T, Takahashi S, Kume H, Takeuchi T, Kitamura T, Homma Y. Cancer-related pain and quality of life in prostate cancer patients: assessment using the Functional Assessment of Prostate Cancer Therapy. *Int J Urol*. 2009;16(5):522-525.
27. McDougall JA, Bansal A, Goulart BH, et al. The Clinical and Economic Impacts of Skeletal-Related Events Among Medicare Enrollees With Prostate Cancer Metastatic to Bone. *Oncologist*. 2016;21(3):320-326.
28. Hussain M, Fizazi K, Saad F, et al. PROSPER: A phase 3, randomized, double-blind, placebo (PBO)-controlled study of enzalutamide (ENZA) in men with nonmetastatic castration-resistant prostate cancer (M0 CRPC). *J Clin Oncol*. 2018;36(6_suppl):3-3.
29. Saad F, Small E, Hadaschik B, et al. Patient (pt) reported outcomes (PROs) in SPARTAN, a phase 3, double-blind, randomized study of apalutamide (APA) plus androgen deprivation therapy (ADT) vs placebo (PBO) plus ADT in men with nonmetastatic castration-resistant prostate cancer (nmCRPC). *Eur Urol Sup*. 2018;17 (2):e1070-e1071.
30. Center for Drug Evaluation and Research. Multi-discipline review. Rockville (MD): U.S. Food and Drug Administration; 2018 February 14: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/210951Orig1s000MultidisciplineR.pdf. Accessed 2018 Jul 29.
31. Naidoo S, Smith I, Casamayor M. Clinical efficacy and safety of licensed drugs and potential new therapies for non-metastatic castration-resistant prostate cancer: A systematic literature review. *Value Health*. 2017;20 (9):A458.
32. Smith MR, Antonarakis ES, Ryan CJ, et al. ARN-509 in men with high risk non-metastatic castration-resistant prostate cancer. *Eur J Cancer*. 2013;2:S695.

33. Smith MR, Antonarakis ES, Ryan CJ, et al. ARN-509 in men with high-risk nonmetastatic castration-resistant prostate cancer (CRPC). *J Clin Oncol*. 2013;31(6 SUPPL. 1).
34. Smith MR, Antonarakis ES, Ryan CJ, et al. Phase 2 Study of the Safety and Antitumor Activity of Apalutamide (ARN-509), a Potent Androgen Receptor Antagonist, in the High-risk Nonmetastatic Castration-resistant Prostate Cancer Cohort. *Eur Urol*. 2016;70(6):963-970.
35. Smith MR, Liu G, Martin Shreeve SS, et al. A randomized double-blind, comparative study of ARN-509 plus androgen deprivation therapy (ADT) versus ADT alone in nonmetastatic castration-resistant prostate cancer (M0-CRPC): The SPARTAN trial. *J Clin Oncol*. 2014;32(15 SUPPL. 1).
36. Mainwaring P, Liu G, Lee JY, et al. SPARTAN-a randomised doubleblind, comparative study of ARN-509 plus androgen deprivation therapy (ADT) vs ADT alone in non-metastatic castration-resistant prostate cancer (M0-CRPC). *BJU Int*. 2015;4:97.
37. Tosco L, Laenen A, Gevaert T, et al. Neoadjuvant degarelix with or without apalutamide followed by radical prostatectomy for intermediate and high-risk prostate cancer: ARNEO, a randomized, double blind, placebo-controlled trial. *BMC Cancer*. 2018;18(1):354.
38. Small EJ, Saad F, Hadaschik BA, Graff JN, Mainwaring PN, McQuarrie K. Patient reported outcomes (PROS) in spartan, a phase 3, double-blind, randomized study of apalutamide (APA) plus androgen deprivation therapy (ADT) vs placebo plus ADT in men with nonmetastatic castration-resistant prostate cancer (NMCRPC). *J Urol*. 199(4):e703-e704.
39. Haidl F, Heidenreich A, Pfister D. Re: Apalutamide Treatment and Metastasis-free Survival in Prostate Cancer. *Eur Urol*. 2018;10.
40. Aragon Pharmaceuticals. Statistical analysis plan (SAP) version 7.0 SPARTAN (selective prostate AR targeting with ARN-509). Rockville (MD): U.S. Food and Drug Administration; 2017: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/rev_210951_arn-509-003_SAP_Redacted.pdf. Accessed 2018 Jul 29.
41. pan-Canadian Oncology Drug Review manufacturer submission: Erleada (apalutamide), 60mg tables. Janssen Inc. Toronto (ON): Janssen Inc.; 2018 Apr 13.
42. Smith MR, Saad F, Coleman R, et al. Denosumab and bone-metastasis-free survival in men with castration-resistant prostate cancer: results of a phase 3, randomised, placebo-controlled trial. *Lancet*. 2012;379(9810):39-46.
43. Janssen Inc. response to pCODR checkpoint meeting questions on Erleada (apalutamide) for the castration resistant prostate cancer [additional manufacturer's information]. Toronto (ON): Janssen Inc.; 2018 May 28.